

Primary results of the phase 3 peak study of bezuclastinib + sunitinib vs sunitinib monotherapy in advanced gastrointestinal stromal tumors (GIST).

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Background: GIST, the most common mesenchymal malignancy of the gastrointestinal tract, is commonly driven by activating *KIT* mutations. Despite therapeutic advances, treating advanced GIST with *KIT* tyrosine kinase inhibitors (TKIs) remains challenging due to emergence of heterogeneous resistance mutations inadequately addressed by current approved therapies. Bezuclastinib, an oral, selective type 1 TKI, in combination with sunitinib, a type 2 TKI, inhibits common primary and secondary resistance mutations in advanced *KIT*-mutant GIST. The Peak study evaluated efficacy and safety of bezuclastinib + sunitinib vs standard second-line sunitinib monotherapy in patients with advanced GIST who received prior imatinib therapy. **Methods:** Peak was a multipart study: dose confirmation (Part 1a), 2 drug-drug interaction (DDI) assessments (Part 1b; DDI substudy), and a randomized phase 3 (Part 2; abstract focus). Patients were randomized 1:1 to bezuclastinib 600 mg once daily (QD) + sunitinib 37.5 mg QD (n=204) or sunitinib 37.5 mg QD (n=209). Primary endpoint was blinded independent central review (BICR)-assessed median progression-free survival (mPFS). Key secondary endpoints were objective response rate (ORR) per BICR and overall survival (OS). Crossover to combination was permitted at BICR-confirmed progression. **Results:** Patients (N=413) were randomized to either bezuclastinib + sunitinib or sunitinib monotherapy; median (range) age, 63 (30-88) years; 59.6% and 14.0% had activating *KIT* mutations in exons 11 only and 9 only, respectively. The combination significantly improved mPFS (HR, 0.50; 95% CI, 0.39-0.65; $P<0.0001$). mPFS was 16.5 months (95% CI, 13.8-19.2) for the combination vs 9.2 months (95% CI, 7.2-11.0) for monotherapy. ORR significantly improved with the combination vs monotherapy (46% vs 26%; risk difference, 20%; 95% CI, 10.6-28.6; $P<0.0001$). As of Sep 30, 2025, OS data remain immature. Incidence of adverse events (AEs) was similar between arms. Grade (Gr) $\geq$ 3 AEs were comparable, with no significant increase in common sunitinib-associated AEs. Higher rates of Gr $\geq$ 3 ALT/AST elevations and anemia were observed with the combination and were manageable with dose modification. ALT/AST elevations led to bezuclastinib dose reductions in 13.2% and discontinuations in 1.5% of patients in the combination arm; all Gr3 hepatic AEs resolved; no Gr4 events occurred. Additional treatment-emergent AEs leading to discontinuation of either drug in >1 patient in the combination arm were neutropenia (2.9%) and diarrhea (1%). No treatment-related AEs led to death in the combination arm. **Conclusions:** Combined *KIT* inhibition with bezuclastinib + sunitinib significantly improved mPFS vs sunitinib monotherapy, reducing the risk of progression or death by 50% and increasing ORR from 26% to 46%. The combination was well tolerated with no new safety findings. Clinical trial information: NCT05208047. Research Sponsor: Cogent Biosciences, Inc.

Velzatinib (IDRX-42) as 1L or 2L therapy for advanced gastrointestinal stromal tumors (GISTs) by *KIT* mutation status: A subset analysis of the phase 1/1b StrateGIST 1 study.

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Background: Most GISTs present with activating *KIT* mutations (exons 9/11) initially responsive to imatinib, but many progress due to diverse *KIT* resistance mutations (largely in exons 13/14/17/18). Velzatinib (subject to USAN approval), a novel selective *KIT* inhibitor, has broad mutation coverage and robust in vitro/vivo preclinical activity in models with mutations relevant to 1st- (1L) and 2nd-line (2L) GIST. We present results from StrateGIST 1 evaluating the safety and efficacy of velzatinib in patients (pts) with advanced GIST as 1L or 2L therapy by *KIT* mutation status. **Methods:** The study design of StrateGIST 1 has been previously described (Schöffski et al. *J Clin Oncol* 2024). We present updated safety and efficacy data for 1L and 2L pts by *KIT* mutation status treated with velzatinib at the recommended phase 1b dose (RP1bD) of 300-mg tablet or exposure-equivalent 400-mg capsule. **Results:** As of December 15, 2025, 18 pts in 1L and 46 pts in 2L received velzatinib at the RP1bD and were evaluable for the efficacy analysis. In 2L pts, median follow-up (mFU) was 14.7 (95% CI: 12.9, 18.4) mo and median progression-free survival (mPFS) was 13.7 (95% CI: 7.4, 18.4) mo. In 1L, the mFU was 6.4 (95% CI: 1.8, 11) mo, and all pts (18/18) had a reduction in tumor volume, of whom 11 (61%) experienced unconfirmed responses, including 1 complete and 10 partial responses (Table 1). As of the cutoff date, 17 1L pts remained on study treatment. Treatment was well tolerated, with low rates of dose reductions (1L: 0%; 2L: 6%) and withdrawals (1L: 0%; 2L: 4%) due to AEs. **Conclusions:** Velzatinib exhibited promising activity and tolerable safety as 1L and 2L therapy across clinically relevant *KIT* mutations for pts with advanced GIST. These data support further study of velzatinib, including in 1L pts, to address the need for therapeutic options with broad coverage of clinically relevant GIST mutations. This study (NCT05489237) is funded by GSK. Clinical trial information: NCT05489237. Research Sponsor: GSK.

Clinical activity and response by mutation status per mRECIST v1.1. ^a							
	1L total (n=18)	2L total (n=46)	2L Ex 9 mutation only (n=8)	2L Ex 11 mutation only (n=14)	2L Ex 11+ATP- binding pocket resistance mutation (13/14) (n=14)	2L Ex 11+activation loop resistance mutation (17/18) (n=3)	2L Other (including ≥2 resistance mutations) (n=7)
Best overall response, n (%)							
Complete response	1 (6)	2 (4)	0	1 (7)	0	0	1 (14)
Partial response	10 (56)	14 (30)	5 (62)	2 (14)	5 (36)	1 (33)	1 (14)
Stable disease	7 (39)	25 (54)	3 (38)	8 (57)	8 (57)	2 (67)	4 (57)
Progressive disease	0	5 (11)	0	3 (21)	1 (7)	0	1 (14)
Not evaluable	0	0	0	0	0	0	0
Objective response rate, n (%)	11 (61)	16 (35)	5 (62)	3 (21)	5 (36)	1 (33)	2 (29)
(95% CI)	(35.7, 82.7)	(21.4, 50.2)	(24.5, 91.5)	(4.7, 50.8)	(12.8, 64.9)	(0.8, 90.6)	(3.7, 71)

^aIn an efficacy-evaluable population defined as all pts with ≥1 postbaseline disease assessment or prior clinical progression or death.

Phase 3 study (APROMISS) of catequentinib hydrochloride (AL3818) monotherapy in patients with advanced alveolar soft part sarcoma (ASPS).

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Background: To report results from the open-label alveolar soft part sarcoma (ASPS) cohort of the phase III APROMISS trial (NCT03016819) evaluating Catequentinib hydrochloride (AL3818), an oral multitargeted receptor tyrosine kinase inhibitor, in adults with advanced or metastatic ASPS. **Methods:** Adult patients with pathologic and molecularly confirmed advanced ASPS, either treatment-naïve or previously treated (excluding cediranib), were enrolled in the open-label, non-randomized ASPS cohort of the phase III APROMISS trial conducted across the United States, Asia, and Europe. Catequentinib hydrochloride was administered orally at 12 mg once daily in 21-day cycles (14 days on/7 days off) until disease progression, toxicity, or death. The primary endpoint was objective response rate (ORR) assessed per RECIST by Blinded Independent Central Review (BICR) (predefined threshold: 31%). Secondary endpoints included duration of response (DOR) with a predefined target of ≥ 6 months, progression free survival (PFS) and overall survival (OS). **Results:** From July 2017 to August 2022, a total of 56 patients entered the trial; 56 patients were evaluable for the primary endpoint. Median (m-) age was 29.5 years (range: 18 – 66), with 24 female and 32 male. Best overall response included 1/56 complete response (1.8%), 14/56 partial responses (25.0%), 36/56 stable disease (64.3%), and 3/56 (5.4%) progressive disease. RECIST ORR by BICR was 26.8% (95% CI, 15.8–40.3); m-DOR was 22.57 months (95%CI: 10.38–NE). The study data was collected close to 8 years for all patients. mPFS was 18.33 months (95% CI, 14.19–23.13), with 6- and 12-month progression-free rates of 88.77% (95% CI, 76.68–94.79) and 65.54% (95% CI, 50.42–77.06), respectively. mOS was 59.27 months (95% CI, 44.09–NE), with 6- and 12-month overall survival rates of 94.64% (95% CI, 84.30–98.24) and 90.81% (95% CI, 79.30–96.08), respectively. Overall, 27/56 (48.2%) patients experienced grade ≥ 3 treatment-related adverse events, most commonly diarrhea (50.0%), hypertension (44.6%), fatigue (37.5%), nausea (35.7%), and palmar-plantar erythrodysesthesia syndrome (30.4%); one patient (1.8%) had a grade 5 event (respiratory failure). **Conclusions:** Catequentinib hydrochloride demonstrated meaningful antitumor activity and durable responses in adults with advanced ASPS. Despite the ORR of 26.8% slightly below the predefined 31% threshold, disease control was prolonged, with a m-DOR exceeding 22 months. Favorable PFS and OS outcomes, together with a manageable safety profile, support its clinical benefit in this ultra-rare sarcoma. Clinical trial information: NCT03016819. Research Sponsor: None.

Efficacy and safety of vebreltinib in advanced clear cell sarcoma (VEBrant): A multicenter, phase II study.

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Background: Clear cell sarcoma (CCS) is an ultra rare cancer with no established standard systemic therapy of proven efficacy. The c-MET pathway plays an important role in CCS, with MET overexpression frequently observed. Targeted therapy by type Ia MET inhibitor crizotinib revealed a disease control rate (DCR) at 69.2% and objective response rate (ORR) at 3.8%. Vebreltinib is a highly selective type Ib MET inhibitor with verified efficacy in solid tumor harboring MET alterations, such as NSCLC with MET amplification or overexpression. This phase II study aimed to assess the efficacy and safety of Vebreltinib for advanced CCS. **Methods:** Patients (pts) with histopathologically confirmed, unresectable or metastatic CCS were enrolled (NCT07153887), regardless of prior therapy except for any MET inhibitors. Eligible pts received Vebreltinib (200 mg BID) until disease progression, intolerable toxicity, or death occurs. Prior PD1/PDL1 treatment for at least 4 months without tumor reduction are allowed to continue using the same PD1/PDL1 medicine after thorough evaluation by the investigator. Evaluation of tumor response was performed every 2 months. Primary endpoints was ORR per RECIST v1.1. Secondary endpoints included DCR, PFS, OS, 12m-OSR, DoR and treatment safety. MET expression by immunohistochemistry was collected when possible. A Simon's two-stage design was applied: if no responses were seen in the first 13 pts, the study would stop; otherwise, 14 additional pts would be enrolled (total N=27). **Results:** At data cutoff on January 23, 2026, 23 pts were enrolled. Median age was 29 years (range: 16–59), 47.8% were male, 91.3% had prior surgery, and 95.7% received prior systemic therapy. All had metastatic disease, primarily to lung (78.3%), lymph nodes (56.5%), and bone (30.4%). With median follow-up of 134 days and median treatment duration of 103 days, 17 pts were evaluable for response. ORR was 41.2% (7 partial responses) and DCR was 70.6% (7 PR, 5 stable disease), meeting the pre-specified threshold for stage I continuation. Median PFS was 4.14 months (95% CI: 2.3–NA); 6-month PFS rate was 42.8%. Median OS was not reached. Treatment-related adverse events (TRAEs) occurred in 87.0% of pts, mostly grade 1–2. Grade 3–4 TRAEs occurred in 21.7% (n=5; rash n=4, fever n=1). Notably, 4 pts discontinued due to grade 4 rash within 2 weeks of starting vebreltinib combined with immunotherapy. **Conclusions:** Vebreltinib demonstrated notable antitumor activity for advanced CCS, representing a marked improvement over existing therapeutic options. Attention should be paid to the risk of severe rash, particularly when combined with immunotherapy. Longer follow-up is required to further confirm the efficacy and safety. Clinical trial information: NCT07153887. Research Sponsor: Beijing Pearl Biotechnology Co., Ltd.

The tetravalent death receptor 5 (DR5) agonist ozekibart (INBRX-109) in conventional chondrosarcoma (CS): Secondary efficacy endpoints from the randomized, registrational, phase 2 ChonDRAGON study.

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Background: Clinical outcomes for unresectable/metastatic CS are poor. There are no approved therapies, and systemic treatment options are limited. Ozekibart (INBRX-109), a novel tetravalent DR5 agonist, was evaluated in ChonDRAGON (phase 2; NCT04950075), the largest randomized, placebo (PBO)-controlled trial in advanced conventional CS. ChonDRAGON met its primary endpoint: ozekibart significantly prolonged median progression free survival (PFS) vs PBO (5.52 vs 2.66 mo; stratified HR, 0.479; 95% CI, 0.335–0.684; $P < .0001$) (Jones et al. CTOS 2025). We present additional efficacy data. **Methods:** Eligible patients (pts) were ≥ 18 y with unresectable/metastatic conventional CS; those ≥ 65 y required a BMI < 30 kg/m². Pts with liver conditions associated with increased risk of hepatotoxicity were excluded. Pts were randomized 2:1 to ozekibart 3 mg/kg IV Q3W or PBO and stratified by grade (2 vs 3), IDH mutation status, and prior systemic therapy (No vs Yes). Pts could cross over from PBO to open-label ozekibart upon progression. The primary endpoint was PFS per RECIST 1.1 assessed by real time central independent radiology review (CIRR) in the intention-to-treat population; inter-arm comparison used a stratified log-rank test. The study was powered to detect a HR of 0.571 (90% power; 1-sided family-wise α , 0.025). Secondary efficacy endpoints included overall survival (OS), overall response rate (ORR) per CIRR, quality of life (QOL; EORTC QLQ-C30 pain symptoms and physical functioning scales), duration of response (DOR), and disease control rate (DCR; response, stable disease ≥ 84 days, non-complete response/non-progressive disease). **Results:** Overall, 137 pts were randomized to ozekibart and 69 to PBO; median duration of follow-up was 10.2 and 9.0 mo at the primary analysis (data cutoff: Sep 30, 2025). Median age for ozekibart and PBO was 54.0 y (range, 20–82 y) and 50.0 y (19–91 y), respectively; 70.1% and 60.9% of pts were male. Most pts had grade 2 CS (ozekibart, 70.1%; PBO, 69.6%) and $\approx 40\%$ received prior systemic therapy (42.3%; 40.6%). 18.2% of pts in the ozekibart arm and 4.3% in the PBO arm remain on treatment. Ozekibart demonstrated a manageable safety profile (Jones et al. CTOS 2025) and led to a significantly greater DCR than PBO (54.0% vs 27.5%; $P = .0005$). ORR was 5.8% (8/137; all partial responses) with ozekibart and 0 with PBO ($P = .0433$); median DOR was 11.1 mo. OS data were immature. Ozekibart significantly delayed QOL deterioration vs PBO, in both pain (median time to deterioration, 2.76 vs 1.41 mo; HR, 0.605; $P = .0033$) and physical functioning (2.56 vs 1.41 mo; HR, 0.561; $P = .0007$). **Conclusions:** In addition to a PFS benefit, ozekibart significantly improved DCR and delayed QOL deterioration vs PBO in advanced CS. Ozekibart has the potential to become the first standard of care for a population with high unmet need. Clinical trial information: NCT04950075. Research Sponsor: Inhibrx Biosciences, Inc.

Pooled analyses of clinical outcomes with afamitresgene autoleucel (afami-cel) in metastatic synovial sarcoma.

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Background: Afamitresgene autoleucel (afami-cel) is a melanoma-associated antigen A4 (MAGEA4)-directed genetically modified autologous T cell immunotherapy consisting of CD4 and CD8 positive T cells transduced with a self-inactivating lentiviral vector (LV) expressing an affinity-enhanced T cell receptor (TCR) specific for the human MAGE-A4. Here we report the pooled results of afami-cel in phase 1 and phase 2 trials in patients (pts) with advanced (unresectable/metastatic) synovial sarcoma (SyS). **Methods:** Pts who were HLA-A*02 positive with previously treated, advanced SyS positive for MAGE-A4 received afami-cel after lymphodepleting chemotherapy containing fludarabine and cyclophosphamide. The pooled analyses evaluated overall response rate (ORR) per RECIST v1.1 by investigator review, duration of response (DoR), ORR in sub-populations, overall survival (OS), safety and pharmacokinetics. **Results:** As of May 2025, 153 pts with advanced SyS received afami-cel ($1.00 - 9.99 \times 10^9$ MAGE-A4 TCR positive T cells). The median age was 40 years (range: 13–76 years), 54% of pts were male, and 86% of pts were white. The median MAGE-A4 expression by H-score was 256.0 (range: 60–300). All pts received prior anthracycline and/or ifosfamide therapy and received a median of 2 prior lines of therapy (range: 1–12). ORR by investigator review was 43.8% (95% CI 35.8, 52.0). Responses were observed across all subgroups, including pediatric SyS pts. The median DoR was 7.1 months (95% CI 4.7, 10.6) and ranged from 1 to 58+ months. Median OS was 18.7 months (95% CI: 14.1, 22.5) with 44% of pts censored at the data cut-off. The 12-month or longer and 24-month or longer OS probabilities were 64.4% and 40.5%, respectively. Among the 67 pts who had a RECIST response, the median OS was 37.5 months (95% CI 26.3, 50.5). The most common any-grade non-laboratory TEAEs ($\geq 20\%$ of pts) were cytokine release syndrome (CRS) (73.2%), nausea (64.1%), fatigue (45.8%), pyrexia (33.3%), vomiting (29.4%), constipation (28.1%), diarrhea (27.1%), headache (26.8%), and cough (20.9%). The most common Grade ≥ 3 laboratory TEAEs ($\geq 20\%$ of pts) were lymphopenia, neutropenia, leukopenia, and anemia. Afami-cel persisted long-term, including >3 years. **Conclusions:** To the best of our knowledge, this is the largest dataset of T-cell therapy treated pts with advanced SyS. The magnitude of ORR supported by DOR demonstrated with afami-cel treatment is considered clinically meaningful in this rare pt population with a poor prognosis and limited effective therapies. CRS and cytopenias were common and manageable. Pts with advanced SyS treated with afami-cel had encouraging survival, especially those pts with a RECIST response. Clinical trial information: NCT04044768, NCT03132922 Research Sponsor: Adaptimmune LLC; USWM CT, LLC.

RINGSIDE: A phase 3 randomized, placebo-controlled trial of varegacestat for treatment of progressing desmoid tumors.

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Background: Desmoid tumors (DT) are rare, locally aggressive tumors with few effective treatments. Varegacestat (VAR) is an investigational, once daily, oral gamma secretase inhibitor that previously showed antitumor activity in pts with DT in the RINGSIDE Phase 2 study. **Methods:** RINGSIDE Phase 3 was a double-blind, placebo (PBO)-controlled study in adults with progressing DT per RECIST v1.1 (NCT04871282). 156 pts were randomized 1:1 to once daily oral VAR 1.2 mg (n=79) or PBO (n=77). Imaging-based tumor response was assessed per RECIST v1.1 by blinded independent central review. The primary endpoint was progression-free survival (PFS). Alpha-controlled secondary endpoints were confirmed objective response rate (ORR), change in tumor volume (TV) at Week 24, and change in patient-reported worst pain intensity (WPI) at Week 12. **Results:** Demographics and disease characteristics were balanced between treatment arms. As of Oct 7, 2025, median duration of exposure was 20.3 months (range 0.8 – 34.6) for VAR and 11.1 months (range 0.2 – 34.6) for PBO. VAR demonstrated significantly better PFS compared with PBO (hazard ratio [HR]: 0.16 [95% CI: 0.07, 0.38; $P<0.0001$]). PFS consistently favored VAR in all subgroups analyzed. ORR was significantly better with VAR vs PBO (55.7% vs 9.1%; $P<0.0001$), with 3 CRs in the VAR arm and 1 CR in the PBO arm. Median duration of response was not reached in either arm. All alpha-controlled secondary endpoints demonstrated statistically and clinically significant superiority for VAR compared with PBO (Table). Overall, 95% of adverse events (AEs) were Grade 1-2 and there were no Grade 5 AEs. Grade 3/4 AEs were reported in 57% of VAR pts and 17% of PBO pts. AEs led to dose reduction in 63 (80%) VAR pts and 7 (9%) PBO pts; 16 (20%) VAR pts and 5 (7%) PBO pts discontinued due to AEs. In the VAR arm, the most frequently reported AEs were diarrhea (82%), fatigue (44%), and rash (43%). Ovarian toxicity occurred in 20/36 (56%) premenopausal women on VAR, resolved in 11/20 (55%), and did not lead to dose interruption or drug withdrawal. **Conclusions:** VAR demonstrated statistically significant and clinically meaningful antitumor activity and pain relief, achieving the highest ORR reported in a Phase 3 trial of systemic DT therapy, with no new safety signals. Clinical trial information: NCT04871282. Research Sponsor: Immunome Inc.

RINGSIDE phase 3 trial outcomes.			
	VAR (n=79)	PBO (n=77)	HR (95% CI) or Difference; P value
Median PFS (95% CI) - radiographic, months	NE (NE, NE)	24.9 (13.8, NE)	0.16 (0.07, 0.38); $P<0.0001$
Confirmed ORR, n (%)	44 (55.7)	7 (9.1)	$P<0.0001$
TV change (cm ³) at Week 24, LS mean (SE)	-109.6 (40.64)	122.8 (42.72)	-232.4 (57.39); $P<0.0001$
WPI (pain) change at Week 12, LS mean (SE)	-2.24 (0.27)	0.18 (0.27)	-2.42 (0.37); $P<0.0001$
Median best % change in TV*	-83.4	11.3	*
1-year PFS, % (95% CI)*	94.2 (85.3, 97.8)	65.6 (52.3, 76.0)	*
2-year PFS, % (95% CI)*	88.9 (77.9, 94.6)	56.7 (42.6, 68.6)	*

LS, least square; SE, standard error.
*Not alpha-controlled endpoint.

Trabectedin with concomitant radiotherapy in resectable retroperitoneal L-sarcoma: A multicenter, prospective, phase I/II trial—A collaborative study by the Spanish (GEIS), Italian (ISG), and French (FSG) groups.

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Background: Liposarcoma (LPS) and leiomyosarcoma (LMS) account for most retroperitoneal sarcomas. Despite complete resection, local recurrence remains high, particularly in dedifferentiated LPS (DDLPS). While preoperative radiotherapy (RT) may improve local control, optimal multimodal strategies are undefined. Trabectedin (T) is active in L-sarcomas, with emerging clinical evidence supporting its radiosensitizing properties and its efficacy in combination with RT. A preoperative short course of T with concurrent low-dose RT was investigated in a multicenter, phase I/II trial in patients (pts) with centrally confirmed resectable retroperitoneal L-sarcoma (grade 2–3 DDLPS with >30% dedifferentiated component or grade 2–3 LMS). **Methods:** Pts received 3 cycles of T in combination with RT (45 Gy in 25 x 1.8 Gy). Phase I followed a 3+3 dose-escalation design with T dose levels 1.5 (0), 1.3 (–1), and 1.1mg/m² (–2). Dose-limiting toxicity was any grade ≥3 adverse events (excluding neutropenia <5 days, elevated transaminases without treatment delay, and nausea/vomiting due to inadequate prophylaxis). Phase I primary endpoint was safety and the determination of the recommended Phase II dose (RP2D). Phase II primary endpoint was centrally assessed Choi response. Secondary endpoints included relapse-free survival (RFS; from surgery), progression-free survival (PFS; from first T cycle), overall survival (OS), RECIST and pathological response, and treatment-related toxicity according to CTCAE v5.0. **Results:** From February 2019 to January 2025, 56 pts, 6 in phase I and 50 in phase II, (M/F: 31/25) with a median age of 61 years (range: 19–75) and a median tumor size of 17 cm (range: 12–30) were enrolled. 51 pts had grade 2–3 DDLPS, and 5 pts had grade 2–3 LMS. A T dose of 1.5 mg/m² was the RP2D. Per-protocol therapy was completed in 47 pts (84%); discontinuations were due to local progression (N=1), toxicity (N=6), or refusal (N=2). The most common grade 3/4 toxicities were neutropenia (21.4%), leukopenia (8.9%), fatigue (8.9%), and increased ALT, febrile neutropenia, and thrombocytopenia (7.1% each). 51 pts (91%) underwent surgery, with 96% achieving complete resection. According to the central review, Choi (N=45) showed 12 PR (26.7%) and 33 SD (73.3%). RECIST 1.1 (N=53): PR 1 (2%), SD 51 (96%), PD 1 (2%). At a median follow-up of 40 months (95% CI, 36–43), from the start of T (N=53), 3-year PFS was 70% (95 CI, 56–83) and 3-year OS was 85% (95 CI, 75–95). **Conclusions:** Preoperative concurrent T and RT was feasible and safe for resectable retroperitoneal L-sarcomas, yielding density responses in over 25% of pts and promising survival outcomes. A phase III trial is warranted to compare this regimen against RT alone. Clinical trial information: NCT02275286. Research Sponsor: Pharmamar.

Final results of a randomized phase II trial of second-line treatment for advanced soft tissue sarcoma comparing trabectedin, eribulin, and pazopanib: 2ND-STEP study, JCOG1802.

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Background: The optimal second-line treatment for advanced soft tissue sarcomas (STS) after doxorubicin therapy remains unclear. This trial aimed to identify the most promising agent among trabectedin, eribulin, and pazopanib for subsequent phase III comparison against gemcitabine plus docetaxel (GD), which has traditionally been considered a standard treatment. We previously reported the results of the primary analysis at 6 months after accrual completion. Here, we present the final analysis results with an additional year of follow-up. **Methods:** This multicenter, randomized, phase II selection design trial enrolled patients with unresectable or metastatic STS who were refractory to doxorubicin-based chemotherapy. Participants were randomized to receive trabectedin, eribulin, or pazopanib. The primary endpoint was progression-free survival (PFS); secondary endpoints included overall survival (OS), disease control rate (DCR), objective response rate (ORR), and safety. **Results:** From December 2019 to March 2023, 120 patients with advanced STS were enrolled (31 leiomyosarcomas, 26 liposarcomas, 18 translocation-related sarcomas, and 45 other types). The median PFS was 2.9 months (95% CI, 1.3–5.3) for trabectedin, 2.2 months (1.5–3.8) for eribulin, and 3.8 months (2.3–5.2) for pazopanib. The hazard ratios for eribulin and pazopanib compared to trabectedin were 1.22 (0.77–1.94) and 0.99 (0.63–1.56), respectively. When examining the PFS curves for each treatment arm, the three arms appeared to exhibit nearly identical curves; however, the PFS hazard ratio indicated that pazopanib showed the best result. The median OS was 14.7 months (10.8–18.5) for trabectedin, 13.3 months (7.6–20.1) for eribulin, and 15.7 months (9.7–18.0) for pazopanib. The DCR was 50.0% (32.4–67.6) for trabectedin, 37.1% (21.5–55.1) for eribulin, and 64.9% (47.5–79.8) for pazopanib. The ORR was 17.6% (6.8–34.5) for trabectedin, 5.7% (0.7–19.1) for eribulin, and 8.1% (1.7–21.9) for pazopanib. A histological subtype-specific subgroup analysis, demonstrated that the PFS/OS for each arm in liposarcoma were as follows: trabectedin, 3.1 months (95% CI, 1.1–7.2) / 12.9 months (3.7–36.5); eribulin, 3.8 months (1.1–6.8) / 13.3 months (4.3–20.1); and pazopanib, 5.2 months (2.0–10.2) / 18.0 months (4.1–NE). No previously unrecognized adverse events related to the investigational drugs were observed, and no treatment-related deaths occurred. **Conclusions:** Consistent with the primary analysis, pazopanib generally showed favorable PFS, OS, and DCR among the three agents. Based on these results, pazopanib was identified as the most appropriate candidate to be compared with GD in a phase III trial, which is currently being planned. Clinical trial information: jRCTs031190152. Research Sponsor: Japan Agency for Medical Research and Development (AMED).

Spatial RNA–protein profiling of antibody–drug conjugate (ADC) targets in leiomyosarcoma (LMS).

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Background: LMS remains a therapeutically challenging sarcoma with limited targeted options. Although ADCs are a promising strategy, none are FDA approved for sarcoma. Prior studies relying on bulk RNA or single-marker immunohistochemistry fail to capture spatial localization, co-expression, and intratumoral heterogeneity. **Methods:** LMS tissue microarrays were profiled using GeoMx DSP to generate spatial RNA and protein expression of ADC targets across multiple regions of interest (ROIs) per tumor. Cases were classified as soft-tissue (ST-LMS; n=23 patients; 94 ROIs) or uterine LMS (U-LMS; n=32 patients; 92 ROIs). A prespecified panel of 35 clinically relevant ADC targets was interrogated. Expression values were normalized to house-keeping genes with group-level scaling. Unsupervised clustering grouped ROIs by spatial expression. Intratumoral and inter-tumoral heterogeneity was quantified using coefficients of variance (CV) across ROIs. RNA–protein concordance and dual target co-expression were quantified using Spearman correlation (ρ). Survival differences between high- and low-expression groups, dichotomized by the median, were evaluated using Kaplan–Meier analysis. **Results:** Of the 35 ADC targets interrogated, 33 were evaluable at the RNA level and 10 at the protein level. Spatial profiling identified four distinct expression clusters. At the RNA level, F3, AXL, and PTK7 showed the highest expression, whereas CDH11, CD99, and ITGA11 exhibited lower expression. At the protein level, Tissue Factor, AXL, and CD70 showed the highest expression, while HER2, and CD99 were lower. Most ADC targets exhibited positive $\log_{10}$ (CV) values, indicating substantial spatial variability. Across most targets, U-LMS showed greater intratumoral and intertumoral heterogeneity than ST-LMS. RNA–protein concordance was greatest for CD99, CD47, and Fibronectin/EDB ($\rho=0.44–0.69$) and minimal for PDGFRA, AXL, ERBB2, EGFR, and MET ($\rho=-0.15–0.19$). RNA co-expression identified seven significant pairs in ST-LMS (e.g., ROR2–FAP, $\rho=0.54$) and eighteen in U-LMS, including MRC2–CD248 ($\rho=0.73$). Dual protein co-expression revealed a strong ERBB2–EGFR correlation in both ST and U-LMS ($\rho=0.79–0.81$), with moderate correlations of these two ADC targets to PDGFRA, AXL, and Tissue Factor ($\rho=0.53–0.70$). High expression levels CD47 and AXL were associated with improved survival in ST-LMS (CD47 HR = 0.76, 95% CI 0.08–0.88, $p = 0.021$; AXL HR = 0.67, 95% CI 0.07–0.72, $p = 0.0067$). **Conclusions:** This study provides the first spatially resolved RNA–protein map of ADC targets in LMS, revealing differential expression, spatial heterogeneity, variable RNA–protein concordance, dual co-expression patterns, and survival associations. These findings establish a foundation for rational ADC development, biomarker-driven patient stratification, and dual ADC combination strategies in LMS. Research Sponsor: None.

Phase 1/2 study of YL201, an anti-B7H3 antibody–drug conjugate (ADC), in patients with relapsed or refractory (R/R) Ewing sarcoma and chondrosarcoma.

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Background: The prognosis for R/R sarcoma remains dismal with limited effective treatment options. YL201 is a B7H3–targeting ADC with promising activity in multiple advanced solid tumors. Here, we report the safety and preliminary efficacy of YL201 monotherapy in patients with Ewing sarcoma (EWS) and chondrosarcoma (CHS) from a phase 1/2 study. **Methods:** Patients with histologically confirmed sarcoma who had an ECOG PS of 0 or 1 and progressed on ≥ 1 prior line of systemic therapies were enrolled and treated with YL201 intravenously Q3W at 2.0 mg/kg or 2.4 mg/kg until disease progression or unacceptable toxicity. The primary endpoint was objective response rate (ORR) per RECIST v1.1. Secondary endpoints included disease control rate (DCR), duration of response (DoR), progression-free survival (PFS), overall survival (OS), and safety. **Results:** Thirty-two patients with sarcoma were enrolled, including EWS (n=20), CHS (n=10), osteosarcoma (n=1), and soft tissue sarcoma (n=1). The overall population had a median age of 34.0 years (range: 19–69), with 81.3% male and 46.9% having an ECOG PS of 1. Patients had a median of 1 prior line of therapy (range: 1–6), with 96.9% having received prior chemotherapy and 37.5% having received targeted therapy. As of December 12, 2025, the median follow-up was 11.4 months (95% CI: 9.1–13.2). In EWS sub-cohort, the confirmed ORR was 50.0% (95% CI: 27.2–72.8) with a median DoR of 6.5 months (95% CI: 2.8–NR), and DCR was 95.0% (95% CI: 75.1–99.9). Median PFS was 5.5 months (95% CI: 2.8–7.9), while OS data remained immature. In CHS sub-cohort, antitumor activity was observed with a confirmed ORR of 10.0% (95% CI: 0.3–44.5) and a DCR of 90.0% (95% CI: 55.5–99.7). The median PFS was 11.7 months (95% CI: 3.9–NR), and median OS was not reached. Membrane B7H3 expression was detected by immunohistochemistry in 42.1% of EWS and 44.4% of CHS patients, whereas the remainder exhibited no membrane B7H3 expression. However, no association was observed between tumor response and B7H3 expression level in either sub-cohort. Among all 32 patients enrolled, the treatment-related adverse events (TRAEs) of any grade and grade ≥ 3 occurred in 100.0% and 34.4% of patients, respectively. The most common grade ≥ 3 TRAEs included lymphopenia (15.6%), neutropenia (9.4%), thrombocytopenia (9.4%), leukopenia (6.3%), and anemia (6.3%). No interstitial lung disease or pneumonitis was observed. The rate of treatment discontinuation due to TRAEs was low at 3.1%, and no treatment-related deaths were reported. **Conclusions:** YL201 showed promising antitumor activity and manageable safety profile in patients with R/R EWS and CHS, with a particularly encouraging ORR in EWS. Given the high incidence of Ewing sarcoma in adolescents, these findings support further evaluation of YL201 in pediatric populations. Clinical trial information: NCT06057922. Research Sponsor: MediLink Therapeutics.

Overall survival analysis of a heavily pretreated population of patients with bone sarcomas treated with mecbotamab vedotin, a conditionally binding ADC targeting AXL.

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Background: Patients with metastatic bone sarcomas continue to lack effective therapies. AXL, a cell-surface receptor tyrosine kinase, is highly expressed in bone sarcoma subtypes and has been shown to drive increased metastasis, resistance to chemotherapy, and poor outcomes. Mecbotamab vedotin (Mec-V, BA3011, Conditionally Active Biologic CAB-AXL-ADC) is designed to reduce off-tumor toxicity and improve pharmacokinetics by conditionally binding to AXL under low-pH conditions (pH<6.7) of the tumor microenvironment. **Methods:** A phase 1/2 open-label study evaluated Mec-V among adult and adolescent patients with AXL-expressing locally advanced, unresectable, or metastatic osteosarcoma, Ewing sarcoma, chondrosarcoma, and chordoma with measurable disease by RECIST v1.1. Patients received Mec-V monotherapy intravenously 1.8 mg/kg every 2 weeks (Q2W). **Results:** This report focuses upon the long term follow up among 33 patients treated with Mec-V with osteosarcoma (n=13), Ewing (n=9), chondrosarcoma (n=8) or chordoma (n=3). Patients received a median of 2 prior lines of treatment. Most related treatment-related adverse events (TEAE) in patients with bone sarcomas were low grade (64%) and reversible; the most common related grade 3/4 TEAE of special interest was neutropenia (18%). No grade 5 TEAE were observed. As of March 25, 2025, disease control rate (DCR) was 100% among patients with chondrosarcoma and chordoma. In patients with osteosarcoma and Ewing sarcoma, DCR was 50% with 3 confirmed responses (14%; osteosarcoma n=2, Ewing n=1). The median OS with Mec-V for all bone sarcoma patients was 17.6 months. Observed median OS by tumor type in months: osteosarcoma (11.9 [95% CI: 3.2-Not Estimable (NE)]), Ewing sarcoma (19.4 [95% CI: 5.2-NE]), chondrosarcoma (NE [95% CI: 16.3-NE]), and chordoma (15.1 [95% CI: 7.2-NE]). **Conclusions:** Patients with treatment refractory bone sarcomas treated with Mec-V monotherapy achieved a median OS of 17.6 months which compares favorably to reported outcomes with other therapies including combination therapies. Mec-V monotherapy holds considerable promise for these high unmet need indications with potential increased benefit when used in combination. Clinical trial information: NCT03425279. Research Sponsor: BioAtla, Inc.

Maintenance treatment with toripalimab and anlotinib after anthracycline-based chemotherapy in patients with advanced soft tissue sarcoma (TORANS): A single-arm, phase 2 trial.

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Background: To date, there is no established maintenance strategy for patients with advanced soft tissue sarcoma (STS) who achieve disease control following first-line anthracycline-based chemotherapy. Maintenance therapy is therefore under active investigation in this setting. This study assessed the efficacy and safety of toripalimab (a humanized anti-PD-1 monoclonal antibody) combined with anlotinib (a multitargeted tyrosine kinase inhibitor) as a maintenance treatment. **Methods:** Patients with advanced STS who achieved stable disease or a partial response after at least four cycles of first-line anthracycline-based chemotherapy were enrolled in this single-arm, phase 2 trial and received maintenance therapy with toripalimab (240 mg intravenously on day 1) and anlotinib (12 mg orally once daily on days 1–14) in 21-day cycles. The primary endpoint was the 24-week progression-free survival rate (PFSR_{24w}), defined as the proportion of patients who remained free from disease progression through 24 weeks after initiation of maintenance therapy. Secondary endpoints included median progression-free survival (PFS), median overall survival (OS), objective response rate (ORR), disease control rate (DCR), and safety. **Results:** Between April 2022 and May 2025, a total of 52 patients were enrolled; one patient diagnosed with pathologically confirmed metastatic carcinoma was excluded. As of December 26, 2025, the median follow-up duration was 20 months. The PFSR_{24w} was 74.5%. The median PFS was 12 months, and the median OS was not reached at the time of data cutoff. Durable partial responses were observed in patients with dedifferentiated liposarcoma (5/14), leiomyosarcoma (2/11), epithelioid sarcoma (2/4), myxofibrosarcoma (1/3), synovial sarcoma (1/3), and pleomorphic rhabdomyosarcoma (1/1), resulting in an ORR of 23.5%. The most common grade 3–4 adverse events were hypertension (n = 10), increased gamma-glutamyltransferase (n = 5), hand-foot skin reaction (n = 3), and hypertriglyceridemia (n = 3). No new safety signals emerged during the course of the trial. **Conclusions:** Toripalimab in combination with anlotinib as maintenance therapy demonstrated promising efficacy and a manageable safety profile in patients with advanced STS following first-line anthracycline-based chemotherapy. Clinical trial information: ChiCTR2100054901. Research Sponsor: The 1·3·5 project for disciplines of excellence—Clinical Research Incubation Project, West China Hospital, Sichuan University (2021HXFH019); 2021HXFH019.

Camrelizumab combined with liposomal doxorubicin and dacarbazine as first-line therapy for advanced, recurrent, and metastatic undifferentiated pleomorphic sarcoma: A phase II study.

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Background: This phase II study aims to evaluate the efficacy and safety of camrelizumab combined with liposomal doxorubicin and dacarbazine in patients with advanced, recurrent and metastatic undifferentiated pleomorphic sarcoma (UPS). **Methods:** Patients with histologically confirmed advanced, recurrent and metastatic UPS, treatment-naïve for advanced disease, and at least one measurable lesion per RECIST v1.1 were eligible. Camrelizumab was administered in combination with liposomal doxorubicin and dacarbazine for up to six cycles, followed by camrelizumab maintenance therapy. The primary endpoint was investigator-assessed objective response rate (ORR) per RECIST v1.1. Secondary endpoints included progression-free survival (PFS), overall survival (OS), duration of response (DoR), and safety. **Results:** Between October 2022 and August 2025, 28 pts were enrolled and received study treatment, of whom 24 were evaluable for efficacy analyses. Partial response occurred in 7 patients, with no complete responses observed, resulting an ORR of 29.2% (7/24). Stable disease was achieved in 14 patients, yielding a disease control rate of 87.5% (21/24). Two patients had progressive disease and four patients were not evaluable due to the absence of post-baseline tumor assessments. With a median follow-up of 11.9 months (data cutoff: December 29, 2025), 16 PFS events and 7 death events had occurred. The median PFS was 8.4 months (95% CI, 6.2-NA), while median OS had not been reached. Responses appeared durable, with a median DoR of 4.5 months among responders (n=7), though early progression was observed in some patients. An exploratory analysis revealed PD-L1-positive patients (CPS ≥ 1) showed a trend toward a higher ORR than PD-L1-negative patients (42.9% [3/7] vs 21.4% [3/14]). The most common treatment-related adverse events of any grade were neutropenia (35.7%), leukopenia (28.6%), rash (28.6%), and ALT elevation (25.0%). Grade ≥ 3 adverse events were infrequent, mainly ALT and AST elevations (both 7.1%). Immune-related adverse events included rash (28.6%), pneumonitis (7.1%), and hepatitis (7.1%), leading to treatment discontinuation in two patients. **Conclusions:** Camrelizumab combined with liposomal doxorubicin and dacarbazine demonstrated promising antitumor activity with durable responses and manageable safety as first-line therapy for advanced, recurrent and metastatic UPS. Exploratory analyses suggested that patients with higher PD-L1 expression may derive greater benefit from this regimen, warranting further investigation in larger, controlled studies. Clinical trial information: ChiCTR2100049974. Research Sponsor: None.

PEMBROCABOSARC: A phase II trial combining pembrolizumab and cabozantinib in patients with advanced undifferentiated pleomorphic sarcoma.

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Background: There is a growing rationale for combining immunotherapy and VEGF inhibitors in sarcoma. We report results of an open-label multicentre phase 2 study assessing the anti-PD-1 antibody pembrolizumab (pembro) in combination with cabozantinib (cabo) in patients (pts) with advanced undifferentiated pleomorphic sarcoma (UPS). **Methods:** Pts aged > 18 years old, with advanced or metastatic UPS who received no more than three previous lines and no previous history of exposure to anti PD1/L1 or cabozantinib were included to receive cabo 40 mg daily and pembro 200 mg IV q21 days. The primary endpoint was 6-month non-progression (NP) per RECIST v1.1. This trial used a 2-stage optimal Simon's design needing 8 NP at 6 months observed among 29 evaluable pts to be considered positive. **Results:** 33 pts were enrolled from December 27th, 2022 to September 25th, 2024, 32 were assessable for safety and 31 for efficacy. Overall, 13 (40.6%) pts had at least one dose reduction of cabo and 5 (15.6%) stopped treatment for a drug-related adverse event (3 related to cabo, 1 to pembro and 1 to both drugs). The most frequent adverse events related to treatment were asthenia, diarrhea, palmo-plantar syndrom and aminotransferase increase. There was no new emerging toxicity with the combination. One grade 5 pneumothorax was considered possibly related to cabozantinib by the investigator. At a median follow up of 13.8 months [95% CI: 12 – 17.2], 8 pts out of the first 29 evaluable pts were NP at 6 months (27.6% [95% CI: 12.7%-47.2%]). Among the efficacy population, 14 pts experienced tumor shrinkage resulting in a partial response (PR) in 8 (25.8%). Responses were long-lasting. The median overall survival was not reached. **Conclusions:** Combining VEGF and PD-1 inhibition showed favorable activity in unselected UPS compared to available evidence for each treatment in monotherapy. Correlative studies of immune biomarkers on paired tumor biopsies and plasma samples done at baseline and on-treatment are on-going to decipher biomarkers of response and resistance to treatment. Clinical trial information: NCT05182164. Research Sponsor: IPSEN; MSD.

Number of patients with at least one Grade 3 to 5 adverse event related to treatment.		
Adverse Event	Grade 3	Grade 5
Diarrhea	2 (6.2%)	0
Palmo-plantar syndrom	2 (6.2%)	0
Aminotransferase increase	2 (6.2%)	0
Hypertension	1 (3.1%)	0
Headache	1 (3.1%)	0
Dysgeusia	1 (3.1%)	0
Skin rash	1 (3.1%)	0
Pyoderma	1 (3.1%)	0
Left ventricular dysfunction	1 (3.1%)	0
Pneumothorax	1 (3.1%)	1 (3.1%)

Toxicity and efficacy characterization of doxorubicin and trabectedin association versus doxorubicin alone in patients over 70 years with leiomyosarcoma: Analysis from LMS02 and LMS04 studies.

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Background: LMS02 (phase II) and LMS04 (randomized phase III) trials demonstrated the superiority of a combination regimen with Doxorubicin (Doxo, 60 mg/m²) and Trabectedin (Trab, 1.1 mg/m²) D1-D21 (Doxo+Trab) versus Doxorubicin (Doxo, 75 mg/m²) alone in the first line setting for metastatic or unresectable leiomyosarcomas with median Overall Survival (mOS) of 33 months (95% CI 26-48 months) versus 24 months (95% CI 19-31 months) (HR for death 0.65; 95% CI 0.44-0.95), respectively. The incidence of adverse events (AE), notably Grade 3-4 AE, was higher with the combination regimen compared to Doxo alone (97% versus 56%, $p < 0.001$, respectively), although these were manageable. As more than one-third of soft-tissue sarcomas occur in patients (pts) over 65-year-old (yo), a better understanding of the risks and benefits of Doxo+Trab association in elderly patients is needed. **Methods:** Data from case report forms of pts aged ≥ 70 years enrolled in LMS02 and LMS04 were retrospectively analyzed to assess efficacy and toxicity of Doxo+Trab versus Doxo monotherapy. **Results:** 44 pts of 70 yo and older were included: 13 pts in LMS02 (Doxo+Trab 6 cycles, without maintenance), 15 pts in LMS04 arm B (Doxo+Trab : 6 cycles, followed by Trab maintenance for up to 17 cycles), and 16 pts in LMS04 arm A (Doxo monotherapy). The mean age was 74 yo (range 70-86), all pts had ECOG PS 0-1, and lung was the most frequent metastatic site. Median OS was 24 months with Doxo, 39 months with Doxo + Trab, and 48.9 months with Doxo + Trab-Trab (LMS04 cohort). Median PFS was 6.7 months with Doxo, 13.2 months in the Doxo + Trab arm, and 20.5 months with Doxo + Trab - Trab Toxicity analysis included patients from LMS02 and LMS04 as follows: 28 pts treated with Doxo+Trab (from both LMS02 and LMS04) and 16 pts treated with Doxo monotherapy in LMS04. The median number of received cycles was 6 in both groups. Twenty-two pts (80%) treated with the combination experienced Grade ≥ 3 AE, including 13 pts with Grade 4 events. These toxicities were predominantly hematologic; with 12% febrile neutropenia and 9% asthenia. In the monotherapy arm, ten pts (63%) had Grade ≥ 3 AE, including 5 pts with Grade 4 events, with asthenia (17%) and febrile neutropenia (17%) being the most frequent. The lack of statistical significance ($p=0.2$) should be interpreted cautiously due to limited sample size. **Conclusions:** For pts over 70 yo, the efficacy of the combination Doxo+Trab followed by trabectedin maintenance in advanced LMS in the first line setting, as measured by PFS and OS, did not differ from that in younger patients. Toxicity analysis suggests that age alone is not a limiting factor for this combination. Therefore, age-related frailty should not prevent patients from receiving a potentially life-prolonging treatment. A global geriatric evaluation and active supportive care may make treatment safer. Research Sponsor: None.

Phase 1 study results with PRAME-directed T-cell receptor (TCR) T-cell therapies in synovial sarcoma.

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Background: Patients with advanced or recurrent synovial sarcoma (SS) have limited treatment options that can provide sustained disease control beyond 6 mos. SS expresses multiple cancer testis antigens, including PRAME, which is expressed in >50 cancers. Anzutresgene autoleucel (anзу-cel, IMA203) is a PRAME-directed TCR T-cell therapy engineered to recognize an intracellular PRAME-derived peptide presented by HLA and initiate a potent and specific antitumor response. IMA203CD8 is a TCR T-cell therapy that additionally engineers a CD8 co-receptor to allow both CD4+ and CD8+ T cells to detect and destroy PRAME-expressing tumor cells that evade conventional therapeutic approaches. Here we present phase 1 results for the subset of pts with SS from IMA203-101 treated with anзу-cel or IMA203CD8 (hereafter TCR T). **Methods:** Pts were ≥ 18 y, HLA-A*02:01+, PRAME+, with R/R solid tumors, measurable disease (RECIST 1.1), ECOG PS 0-1, and no remaining SOC treatment options. Following leukapheresis and TCR T manufacture, pts underwent lymphodepletion (LD) with Cy ($500 \text{ mg/m}^2 \times 4 \text{ d}$) and Flu ($30 \text{ mg/m}^2 \times 4 \text{ d}$), followed by TCR T infusion +/- low-dose SUBQ IL-2. **Results:** As of Oct 27, 2025, 21 pts with SS were treated with anзу-cel (n=9) or IMA203CD8 (n=12). The most common TEAEs were LD-related cytopenias (100%). Cytokine release syndrome occurred in 18 pts (86%; G1: 38%, G2: 38%, G3: 10%). One event of G1 immune effector cell-associated neurotoxicity occurred (5%). Twenty pts were evaluable for efficacy and received a low median dose of 1.51×10^9 total TCR T cells (range: $0.35\text{--}9.36 \times 10^9$). These pts had a median sum of target lesions at baseline of 10.22 cm (range: 1.24-41.1 cm) and received a median of 2.5 prior lines of therapy (range: 1-5). At baseline, 65% had ≥ 2 previous lines of systemic therapy and 75% received prior radiotherapy. The confirmed objective response rate (cORR), including all pts evaluable for efficacy across escalating doses, was 50% (10/20), including 1 confirmed CR (8%) with IMA203CD8 at a dose of 2.05×10^9 total TCR T cells. Median tumor reduction for pts with confirmed objective response was -63.4%. Median duration of response at these escalating dose levels was 12.7 mo (mFU: 23 mo) with 5 responses lasting for ≥ 12 mo including 2 ongoing PRs at 27 and 23 mo. Median overall survival was 18 mo. Results include 1 pt who received 3 sequential TCR T-cell therapies: the MAGE-A4-targeted afamitresgene-autoleucel (BOR: SD; PFS: 21.4 mos), PRAME-targeted anзу-cel (BOR: cPR; PFS: 24.4 mo), and IMA203CD8 (BOR: cPR; PFS ongoing at 24.4 mo). **Conclusions:** PRAME-directed TCR T-cell therapies exhibited a safety profile consistent with previous observations, and despite low doses, promising antitumor activity with durable responses that deepened over time in pts with SS. These results warrant further investigation. Clinical trial information: NCT03686124. Research Sponsor: None.

Longitudinal plasma and CSF ctDNA profiling as used to define therapeutic landmarks and compartmentalized clonal evolution in rhabdomyosarcoma.

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Background: Current risk stratification in rhabdomyosarcoma (RMS) relies on static pretreatment variables, which fail to capture dynamic tumor evolution and molecular residual disease under therapeutic pressure. Although liquid biopsy offers a non-invasive solution, clinical implementation has been constrained by a reliance on retrospective datasets and the lack of prospectively validated therapeutic landmarks or compartmentalized monitoring strategies. **Methods:** We conducted the largest multi-center, prospective liquid biopsy study to date, enrolling 143 treatment-naïve RMS patients (Aug 2020–Feb 2025; 91.6% intermediate/high-risk). We utilized ultra-deep ($>5,000\times$) sequencing (506-gene panel) on matched tumor, longitudinal plasma (n=292), and cerebrospinal fluid (CSF) from patients with parameningeal or central nervous system (CNS) metastatic disease. Critically, paired tissue and plasma were collected at disease progression (PD) to map evolutionary trajectories. Genomic alterations were correlated with progression-free survival (PFS) and overall survival (OS) using univariate and multivariate Cox regression. **Results:** Baseline profiling identified MYOD1 mutation as the strongest independent predictor of inferior PFS (HR 6.52, $P=0.003$), while MYCN amplification defined a novel "ultra-high-risk" fusion-positive subset (OS, $P<0.001$). Baseline ctDNA positivity (66.7%) correlated with advanced disease ($P<0.001$). Longitudinally, persistent ctDNA at Cycle 5 Day 1 (C5D1) conferred a 12-fold increased progression risk (HR=12.2, $P=0.004$), establishing C5D1 as the definitive prognostic landmark. Patients with positive longitudinal ctDNA harbored a nearly 6-fold increased risk of progression (HR = 5.97, 95% CI 2.25–15.85, $P < 0.001$) and a 12-fold increased risk of death (HR = 12.4, 95% CI 1.42–108.37, $P = 0.023$) compared to those with sustained negativity. Analysis of paired samples at relapse revealed subclonal replacement driven by therapeutic pressure, enriching for acquired resistance alterations in TP53 and DNA damage response (DDR) pathways undetectable by static assays. Additionally, paired CSF-plasma profiling in parameningeal/CNS disease identified the CNS as an evolutionary "sanctuary site" harboring distinct, compartment-specific drivers (e.g., TP53, HRAS) divergent from plasma. **Conclusions:** This prospective study establishes ctDNA as a critical biomarker for RMS, defining MYOD1, MYCN, and TP53 as key genomic risk factors and validating C5D1 as the optimal therapeutic landmark. Deep longitudinal profiling uncovers subclonal replacement and compartmentalized CNS evolution as drivers of treatment failure, advocating for comprehensive, compartment-specific monitoring in next-generation risk-adapted trials. Clinical trial information: NCT05778955. Research Sponsor: None.

Safety and pharmacokinetics (PK) of lurbinectedin (lurbi) in pediatric patients (pts) with relapsed/refractory (R/R) solid tumors and preliminary antitumor activity in pediatric and young adult pts with R/R Ewing sarcoma (EwS): Results from a phase 1 study.

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Background: About 30% of pediatric cancers are solid tumors. EwS is the second most common bone tumor among children and young adults; 5-year survival rates for R/R EwS are <15%. Lurbi is a trabectedin analogue that alkylates DNA and blocks transcription of EWS-FLI1, a primary driver of EwS. In a phase 2 basket trial, lurbi demonstrated an objective response rate (ORR; complete response [CR] or partial response [PR]) of 14% and disease control rate (DCR; CR, PR, or stable disease) of 57% in 28 adults (median age, 33 years [y]) with R/R EwS. Here, we report phase 1 results from a multicenter, open-label study (NCT05734066) of lurbi in pediatric and young adult pts with R/R solid tumors including EwS. **Methods:** Part 1 evaluated the safety, tolerability, PK, and recommended phase 2 dose (RP2D) of lurbi monotherapy in pediatric pts (aged 2–18 y) with R/R solid tumors. RP2D selection used a Bayesian optimal interval design starting with the approved adult dosage, 3.2 mg/m² lurbi IV over 1 hour every 3 weeks. Two additional cohorts were treated at the RP2D: a safety cohort for pts aged <18 y and a histology-specific safety and efficacy cohort for pts aged 2–30 y with R/R EwS. Tumor responses were assessed every 6 weeks per RECIST v1.1. **Results:** As of Oct 22, 2025, 21 pts received ≥1 dose of lurbi (3.2 mg/m², n = 17; 4.0 mg/m², n = 4). Median (range) age was 16 (10–25) y; 13 (62%) pts had received ≥3 prior lines of treatment (Tx). Median (range) lurbi cycles administered was 3 (1–18); 3 (14%) pts were still receiving lurbi; 18 (86%) discontinued Tx. At 4 mg/m², dose-limiting pulmonary edema and rhabdomyolysis/acute kidney injury were observed. Among pts receiving lurbi 3.2 mg/m², 8 (47%) had grade ≥3 Tx-related adverse events (TRAEs); anemia (5 [29%]) and platelet count decrease (5 [29%]) were most common (Table). For pts aged ≥6 y, the RP2D was 3.2 mg/m²; accrual of pts aged <6 y is ongoing to determine RP2D. Although geometric mean (Geo CV%) C_{max} (163 µg/L [105%]) and AUC_{inf} (1893 µg·h/L [126%]) were higher in children/young adults vs adults in the phase 2 basket trial (increased 53% and 244%, respectively), there was substantial overlap in drug exposures. Among 11 evaluable pts with R/R EwS receiving lurbi 3.2 mg/m², the confirmed ORR was 18%, and the DCR was 55%; 2 responders were progression free at their last assessments (5.7 and 6.9 months). **Conclusions:** Based on these data, lurbi had a manageable safety profile, predictable PK properties, and encouraging preliminary clinical activity in pts with R/R EwS. Phase 2 expansion in pts ≤30 y with R/R EwS is ongoing. Clinical trial information: NCT05734066. Research Sponsor: Jazz Pharmaceuticals.

TRAEs in all pts and by dose.			
n (%)	All N = 21	3.2 mg/m ² n = 17	4.0 mg/m ² n = 4
Any TRAE	21 (100)	17 (100)	4 (100)
Grade ≥3	12 (57)	8 (47)	4 (100)
Serious	4 (19)	2 (12)	2 (50)
Led to Tx discontinuation	1 (5)	0	1 (25)
Led to death	1 (5)	0	1 (25) ^a

^aDue to acute kidney injury.

Association of NAB2–STAT6 distal fusion with risk level of metastatic disease and thoracic primary site.

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Background: Solitary fibrous tumors (SFTs) are defined by the NAB2–STAT6 gene fusion, but the clinical significance of these breakpoints remains incompletely understood. Although fusion breakpoint heterogeneity has been implicated in influencing biologic behavior, there are few studies linking variant location to outcomes. Recent genome analyses suggest that proximity based breakpoint clustering approaches can reveal driver loci, suggesting investigation of NAB2–STAT6 fusion breakpoints may be potential prognostic markers. Because individual variants are rare, we used a proximal vs distal breakpoint analysis to evaluate high-risk clinical features. In this study, we evaluated trends between the NAB2–STAT6 breakpoint and metastases, primary tumor location, and recurrence in a single-institution, retrospective cohort study. **Methods:** We performed an analysis of patients with SFTs treated at the Sylvester Comprehensive Cancer Center (n=48). Samples without pathology-confirmed NAB2–STAT6 fusions were excluded. Clinical variables included primary tumor site, size, stage, and recurrence. Molecular data was extracted from next-generation whole transcriptome and exome sequencing reports. Breakpoints were categorized by exon numbers. NAB2 breakpoints were considered proximal if they occurred before exon 6 and distal if they occurred at exon 6 or more distally. STAT6 breakpoints were considered proximal if they occurred at exon 6 or earlier and distal if they occurred at exon 16 or more distally. Associations were analyzed using Fisher exact tests. **Results:** Breakpoint patterns were significantly associated with metastatic presentation at diagnosis. Metastatic disease at the time of diagnosis was not observed in any patients with proximal STAT6 breakpoints (n= 29) but was present in 24% (n = 17) of those with distal STAT6 breakpoints (p=0.02). Additionally, metastatic disease occurred exclusively in tumors with distal NAB2 breakpoints (n=14, p=0.01). Breakpoint patterns were also associated with primary tumor sites. The majority of proximal STAT6 fusions were present mostly in thoracic cavity tumors (55%), while distal STAT6 fusions occurred mainly in tumors at non-thoracic sites (p=0.02). Among fusion subtypes, metastatic presentation was absent in ex4: ex2 tumors but observed in 31% of tumors with ex6: ex16/17 tumors (p=0.02). Distal STAT6 breakpoints also showed trends toward higher recurrence rates and grades as well as larger tumor sizes. **Conclusions:** Our study shows that NAB2–STAT6 distal fusion breakpoint patterns are associated with metastatic disease at diagnosis, non-thoracic primary tumor locations and more aggressive clinical features. These findings support the consideration of breakpoint patterns as part of molecular risk stratification and identifies a potential biomarker for SFT patients with a primary tumor who may benefit from chemotherapy. Research Sponsor: None.

Efficacy of velzatinib (IDRX-42) in patients with advanced/metastatic GIST by line of therapy and circulating tumor DNA response in the phase 1/1b StrateGIST 1 trial.

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Background: Most gastrointestinal stromal tumors (GIST) are driven by mutations in *KIT* or *PDGFRA*. Resistance to standard tyrosine kinase inhibitor (TKI) therapy is largely driven by acquisition of secondary mutations in *KIT* exons 13/14/17/18. Velzatinib (subject to USAN approval) is a broad-spectrum TKI designed to inhibit most common primary *KIT* mutations (exons 9 and 11) as well as secondary mutations. We present updated circulating tumor DNA (ctDNA) results from StrateGIST 1, a phase 1/1b study evaluating the efficacy and safety of velzatinib across primary and secondary mutations in patients (pts) with advanced/metastatic GIST. **Methods:** The study design of StrateGIST 1 has been previously described (Schöffski et al. *J Clin Oncol* 2024). Clinical activity was assessed by mRECIST v1.1. Blood samples for ctDNA analyses (Guardant360 assay) were collected for all pts before and serially during treatment. Data analysis was performed in R and hazard ratios were calculated using Cox proportional hazards regression. **Results:** As of September 2025, 256 pts received velzatinib across all lines of therapy. Velzatinib showed clinical activity against both primary (Exon 9 ORR: 44% [95% CI: 29.1, 60.1]; Exon 11 ORR: 19% [95% CI: 12.7, 27.6]) and secondary (Exon 13 ORR: 17% [95% CI: 8.6, 27.9]; Exon 14 ORR: 20% [95% CI: 2.5, 55.6]; Exon 17 ORR: 23% [95% CI: 14.6, 33.2]) mutations. Clinical activity is supported by ctDNA analysis (n=180 pts); >99% reduction in ctDNA variant allele frequency (VAF) was observed across a broad spectrum of individual mutations (Exon 9: 80%; Exon 11: 67%; Exon 13: 80%; Exon 14: 80%; Exon 17: 83%). We also evaluated the predictive value of different exon mutations in *KIT* detected at baseline via ctDNA. Focusing on pts with primary mutations only, *KIT* exon 9 mutations had 3-fold lower risk of disease progression compared to exon 11 mutations (HR=3.06). No significant difference was observed between major secondary mutations (exon 13 vs exon 17). Additionally, 46 pts without detectable *KIT*/*PDGFRA* mutations at baseline showed a lower progression risk (HR=0.41) compared to 180 pts with detectable *KIT*/*PDGFRA* mutations, underscoring the prognostic and/or predictive value of ctDNA analysis, even in low-shedding indications such as GIST. **Conclusions:** Velzatinib has broad activity against clinically relevant *KIT* mutations in pts with advanced and/or metastatic GIST and can substantially reduce ctDNA levels across a broad spectrum of clinically meaningful *KIT* mutation profiles. Baseline exon-level *KIT* mutation status and ctDNA detectability provide potentially useful prognostic and predictive data, justifying further study to discern the relationship between clinical benefit and molecular response. This study (NCT05489237) is funded by GSK. Clinical trial information: NCT05489237. Research Sponsor: GSK.

Feasibility of constructing an external control arm for early efficacy assessment in phase 1a: Methodological framework from the INVOKE trial.

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Background: Phase 1a dose-escalation trials are primarily designed for safety but often lack sufficient visibility into efficacy signals due to small sample sizes and the absence of a comparator arm. This uncertainty can delay decision-making and increase late-stage failure rates. We hypothesized that a synthetic External Control Arm (ECA) aggregating real-world data (RWD) and historical clinical trials could be established to contextualize efficacy readouts from the ongoing OKN4395 Phase 1a study (INVOKE; NCT06789172; Trial in Progress abstract submitted to this meeting). **Methods:** We curated a retrospective dataset of 298 solid tumor patients derived from two complementary sources, RWD and recent clinical trials (inclusion date $\geq$ 2016). To ensure comparability with the INVOKE population, patient selection adhered strictly to the study's inclusion and exclusion criteria, with only individuals who had exhausted all standard-of-care (SoC) options being retained. We further refined the cohort to ensure exact overlap, retaining only external patients who shared an identical baseline covariate profile with at least one patient in the INVOKE cohort. Finally, we applied statistical adjustment methods, including Inverse Probability of Treatment Weighting (IPTW) and G-Computation, to align the remaining cohort on major prognostic variables (e.g. ECOG status, prior lines of therapy, inter alia). **Results:** A total of 13 INVOKE patients with available endpoint data were eligible for ECA matching. The selection process yielded a final robust ECA cohort of 40 patients. In this refined population, we achieved robust covariate alignment between the ECA and the INVOKE cohort, with absolute Standardized Mean Difference (SMD) < 0.13 for all major prognostic variables. Despite the methodological differences between IPTW and G-computation, both statistical approaches yielded highly consistent estimates. Data from INVOKE, a study in early stages, is yet to publish data (TIP presented at this meeting), comparative efficacy data will be disclosed at a later date. **Conclusions:** We demonstrated that constructing a synthetic ECA generating outcomes directly comparable to those of the population of an active Phase 1a dose-escalation study is methodologically feasible. The establishment of this matched external cohort and first application to the INVOKE Phase 1a study provides a proof of concept framework for early efficacy assessment. This "de-risking" tool is now positioned to provide rapid, concurrent contextualization of emerging data from the INVOKE trial upon data maturity. Research Sponsor: None.

AI-assisted systematic review and pooled analysis of anthracycline- versus taxane-based chemotherapy in advanced or metastatic angiosarcoma.

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Background: Comparative evidence for first-line anthracycline- (Ant) vs taxane-based (Tax) chemotherapy in advanced angiosarcoma (AS) is limited by small, heterogeneous retrospective studies. We performed an AI-assisted systematic review and pooled analysis to overcome fragmented reporting and evaluate efficacy and safety across clinically relevant subgroups, including cutaneous and radiation-induced AS (RIAS). **Methods:** A PubMed search (2000–2025) identified 11 eligible studies, 6 providing quantitative class-specific outcomes. An AI-assisted workflow (GPT-5) harmonized heterogeneous datasets, resolved denominator inconsistencies, and enabled supervised reconstruction of missing subgroup numerators. Endpoints included objective response rate (ORR), disease control rate (DCR), survival outcomes, and toxicity. ORR and DCR were compared using two-proportion z-tests. PFS, OS, and safety outcomes were summarized descriptively based on reported medians, due to incomplete and heterogeneous reporting that precluded pooling. **Results:** Among 426 evaluable patients (Ant n = 245; Tax n = 181), Tax demonstrated higher pooled ORR (44.8% vs 29.0%, $p = 0.001$) and DCR (63.7% vs 52.6%, $p = 0.018$). Benefits were marked in cutaneous AS (ORR 50.8% vs 31.5%, $p = 0.017$) and RIAS (41.8% vs 30.2%, $p = 0.036$), while non-cutaneous AS showed comparable ORR (25.3% vs 27.8%, $p = 0.68$). Reported median PFS (6.2 vs 5.0 months) and OS (14.3 vs 12.2 months) numerically favored Tax. Safety analysis, enabled by AI integration of fragmented datasets, showed that Tax was mainly associated with low-grade neuropathy and mild myelosuppression. Ant toxicity reporting was sparse but included fatal neutropenic events, indicating greater hematologic risk. **Conclusions:** Tax shows superior antitumor activity in cutaneous AS and RIAS with favorable tolerability. Anthracyclines remain an option for selected patients, although higher hematologic toxicity is expected. These findings, derived through AI-assisted reconstruction of incomplete datasets, highlight both the therapeutic relevance of Tax in AS and the potential of AI to enhance evidence synthesis in rare cancers. Research Sponsor: None.

Efficacy and safety of continuous intra-arterial cisplatin and recombinant human endostatin combined with systemic chemotherapy in osteosarcoma: A phase II study.

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Background: Previous studies have demonstrated that preoperative intra-arterial cisplatin infusion elicits a favorable histologic response—a key prognostic factor for survival in osteosarcoma. Recombinant human endostatin (rh-endostatin; Endostar), an anti-angiogenic agent, has been shown to significantly improve survival when administered intravenously in combination with chemotherapy for osteosarcoma. Herein, we report preliminary results on the efficacy and safety of continuous intra-arterial cisplatin and rh-endostatin combined with systemic chemotherapy in osteosarcoma (NCT06562673). **Methods:** This open-label, single-arm, single-center, phase II clinical trial enrolled patients with histologically confirmed primary localized extremity conventional osteosarcoma. Patients received 2 cycles of high-dose methotrexate and anthracyclines intravenously. Intra-arterial infusion was performed concurrently with anthracyclines. Rh-endostatin was administered intra-arterially (150 mg over 6 hours); then, cisplatin was administered intra-arterially (100–120 mg/m² over 6 hours). Efficacy and safety were evaluated after surgery. **Results:** Ten patients were enrolled from December 2024, to April 2025, including 7 males and 3 females with a mean age of 17.8 years (range, 12–42 years). Tumor locations included the femur (n=6), tibia (n=3), and humerus (n=1). Preoperative arterial infusions were administered 3 times (n=1), 2 times (n=8), and 1 time (n=1). All patients underwent limb-sparing surgery. The tumor necrosis rate was >90% in 5 cases (50%) and ≤90% in 5 cases (50%). Adverse events included grade 3 vomiting and nausea (n=1), grade 1 renal impairment (n=2), fever (n=1), and skin induration (n=1). Due to grade 3 gastrointestinal toxicity observed in the first enrolled female patient, the cisplatin dose was uniformly reduced to 100 mg/m² for all subsequent patients in the trial. **Conclusions:** Intra-arterial administration of high-dose rh-endostatin and cisplatin combined with systemic chemotherapy in osteosarcoma appears safe and achieves a good histologic response rate of 50%, compared with a historical rate of 30% with intravenous chemotherapy alone. Clinical trial information: NCT06562673. Research Sponsor: None.

ICONIC (Improving Outcomes Through Collaboration in Osteosarcoma): Insights from a national prospective cohort trial for newly diagnosed osteosarcoma patients.

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Background: There has been little change in osteosarcoma (OS) treatment over the last two decades. Understanding management patterns, better understanding of biology and identifying new biomarkers are key to improving outcomes. **Methods:** ICONIC is a UK-wide prospective observational trial of newly diagnosed OS pts with longitudinal clinical, imaging, tissue and pt experience data collection to address key objectives. These include describing variation in management and outcomes for specific pt groups, establishing an imaging repository to develop imaging biomarkers, analysis of plasma cfDNA, and use of tumor tissue to develop pt-derived models and decode tumor-immune cross talk. Pts were recruited from Oct 2019 to Jan 2025. Progression-free (PFS) and overall survival were analysed using Kaplan-Meier survival statistics and Cox regression. **Results:** A total of 337 pts were recruited from 27 sites. Median age was 19 (range 3-83); 17% had metastases. In total, 229/253 (91%) pts receiving neoadjuvant treatment had methotrexate, doxorubicin, cisplatin (MAP); 259 underwent surgery, of which 52 (20%) had amputations; 101/161 (63%) of eligible pts received mifamurtide. With median follow-up of 2.5 years, 2-year PFS and overall survival were 57% (95% CI 51-63) and 78% (95% CI 72-83) (Table 1). Age, raised ALP, pelvis or trunk primary sites, metastases and inoperability were associated with worse PFS. Pts with a good pathological response to treatment and ≥2mm resection margin had the lowest risk of local recurrence (p=0.02). A pilot radiomics analysis of 32 pts undergoing resection after MAP, demonstrated baseline tumour volume (p=0.044) pre-treatment T2 Gray Level Non-Uniformity (GLNU) (p=0.002), and post-treatment GLNU difference (p=0.008) to be associated with overall survival. Longitudinal blood samples for cfDNA analysis were collected from 226 pts. Patient-derived primary cultures were successfully developed from 12 pts. Spatially-resolved genomic and transcriptomic analysis of tumor tissue to study genomic evolution and immune evasion is ongoing. **Conclusions:** ICONIC trial has identified variation in management and outcomes of OS, which will guide future practice and provided a successful platform for imaging and biomarker analysis, which is ongoing. Clinical trial information: NCT04132895. Research Sponsor: Bone Cancer Research Trust.

Pt characteristics and outcomes according to age and primary site.					
	All patients N=337	<16 years N=115	16-24 years N=101	25-39 years N=60	>40 years N=61
Lower limb	228 (68%)	90 (78%)	74 (73%)	34 (57%)	30 (49%)
Upper limb	40 (12%)	18 (16%)	9 (9%)	6 (10%)	7 (11%)
Craniofacial	23 (7%)	3 (3%)	6 (6%)	7 (12%)	7 (11%)
Pelvis/sacrum	22 (7%)	1 (1%)	8 (8%)	4 (7%)	9 (15%)
Trunk	12 (4%)	1 (1%)	4 (4%)	5 (8%)	2 (3%)
Unknown	12 (4%)	2 (2%)	0 (0%)	4 (7%)	6 (10%)
Survival outcome analysis					
2-year PFS (95% CI)	57% (51-63)	65% (55-74)	55% (44-66)	60% (45-73)	44% (30-57)
2-year OS (95% CI)	78% (72-83)	77% (66-84)	87% (77-93)	78% (62-88)	64% (49-75)

Efficacy and safety analysis of anlotinib combined with etoposide plus ifosfamide in the treatment of children and adolescents with pulmonary metastatic osteosarcoma.

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Background: Osteosarcoma is a highly malignant and aggressive tumor, predominantly occurring in children and adolescents under 20 years of age. It exhibits early metastatic potential, with 15%–20% of patients presenting with distant metastasis at diagnosis. Among these, pulmonary metastases account for 85% of cases. The 5-year survival rate after pulmonary metastasis is <20%. This study retrospectively analyzes the efficacy and safety of anlotinib combined with etoposide and ifosfamide in treating pediatric and adolescent patients with pulmonary metastatic osteosarcoma. **Methods:** This study retrospectively screened children and adolescent patients with pulmonary metastatic osteosarcoma who received etoposide + ifosfamide ± anlotinib at Northwest Women's and Children's Hospital from May 2018 to December 2024. The study was divided into a combination group (anlotinib + etoposide + ifosfamide) and a control group (etoposide + ifosfamide). The dosage of anlotinib: 8 mg for patients < 12 years old, qd, d1–d14, q3w, 12mg for patients ≥12 years old, qd, d1–d14, q3w. Treatment continued until disease progression or intolerable toxicity, with a maximum of 4 chemotherapy cycles. The primary endpoint of the study was objective response rate (ORR), and secondary endpoints included disease control rate (DCR), progression-free survival rate (PFSR), and safety. **Results:** The data cut-off date was December 2024, The study enrolled 38 patients (combination group: n=18, control group: n=20). Efficacy analysis showed the combination group achieved higher ORR (22.2% vs 15%, p=0.057) and significantly better DCR (66.7% vs 45%, p=0.015), and 3-month progression-free survival rates (PFSR) of 44.0% versus 30%. Subgroup analysis indicated superior outcomes with 12 mg versus 8mg anlotinib (p<0.05). Biomarker evaluation revealed patients with high BRCA1/VEGFR2 expression had lower 3-year survival than those with intermediate/low expression, while low PDGFR expression was associated with poorer survival compared to intermediate/high levels. The combination group exhibited higher incidence rates of treatment-related adverse events (TRAEs) compared to the control group, including epistaxis (44.4%), hand-foot syndrome (27.8%), abnormal thyroid function (22.2%), and proteinuria (16.7%). All reported adverse events were grade 1–2 in severity, with no grade 3–4 severe adverse reactions observed. **Conclusions:** The combination therapy of anlotinib with ifosfamide and etoposide demonstrated superior efficacy compared to chemotherapy alone in pediatric patients with pulmonary metastatic osteosarcoma, showing higher ORR, DCR, and 3-month PFSR. These results indicate that anlotinib combined with neoadjuvant chemotherapy can more effectively delay tumor progression and prolong progression-free survival in these patients. Research Sponsor: None.

Efficacy and safety of perioperative anlotinib combined with cisplatin and doxorubicin in treatment-naïve stage IIB classic osteosarcoma of the extremity: Updated results from the ALTER-S002 trial.

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Background: Clinical studies show overexpression of multiple tyrosine kinase receptors in osteosarcoma, supporting targeted therapy as a promising direction. Anlotinib, a multi-targeted tyrosine kinase inhibitor, exerts anti-tumor angiogenesis effects. Combining anti-angiogenic agents with chemotherapy may yield synergistic tumor control, particularly as perioperative therapy. We present updated long-term efficacy and safety data, including key secondary endpoints, to validate this regimen's clinical value. **Methods:** This was an open-label, single-arm, multicenter phase II trial. Eligible patients (12–40 years) had histologically confirmed primary localized stage IIB classic extremity osteosarcoma and were operable. Patients received anlotinib (10mg, po, d1–14, q3w), doxorubicin (A, 20–25 mg/m², iv, d1–3, q3w) and cisplatin (P, 70–90 mg/m², iv, d1, q3w) for 9 weeks. Radical surgery was performed at week 10 (no contraindications). Postoperatively, A+P was given at weeks 12–14, followed by anlotinib+A+P (same doses) at weeks 15–20. From week 21, anlotinib monotherapy (12mg, po, d1–14, q3w) continued until week 104 or an event-free survival (EFS) event. Primary endpoint: 24-month EFS rate. Secondary endpoints: 36-month EFS rate, local recurrence rate, lung metastasis rate, 3-year overall survival (OS) rate, and safety. **Results:** From May 2020 to April 2022, 52 patients were enrolled, treated, and included in full analysis set (FAS) and safety set (SS). Of these, 84.6% (44/52) were Han and 55.8% (29/52) male. Median follow-up was 42.7 months (IQR 30.4–52.7). The 24-month and 36-month EFS rates were 73.7% (95% CI 59.0–83.9) and 46.6% (95% CI 27.4–63.7), respectively. Median OS was not reached; 36-month and post-hoc 60-month OS rates were 74.6% (95% CI 59.6–84.7) and 71.4% (95% CI 55.5–82.4). Twenty-five percent (13/52) of patients died, mostly due to lung metastasis (13%). Among 51 surgical patients, local recurrence, lung metastasis, and other-site metastasis occurred in 23.5%, 17.6%, and 9.8%, respectively. Median recurrence-free survival (RFS) was 32.4 months (95% CI 25.7–not estimable). Grade 3–4 treatment-related adverse events (TRAEs) occurred in 84.6% (44/52) of patients, with neutropenia most common (28/52 [53.8%]). No grade 5 TRAEs were observed. Serious TRAEs occurred in 40.4% (21/52), mainly myelosuppression (14/52 [26.9%]). None of the 13 on-study deaths were TRAE-related. **Conclusions:** Perioperative anlotinib plus cisplatin and doxorubicin shows promising efficacy in treatment-naïve stage IIB classic extremity osteosarcoma, with manageable safety. It achieves favorable long-term OS, and clinically acceptable local recurrence and lung metastasis rates, serving as a potential new perioperative option for this population. Clinical trial information: ChiCTR 2000033298. Research Sponsor: None.

A phase 2 trial of cetuximab for patients with locally advanced/metastatic chordoma.

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Background: Unresectable/metastatic chordoma is a rare notochordal malignancy with no approved systemic treatments. EGFR is widely expressed on chordomas. Cetuximab is a recombinant, human/mouse chimeric monoclonal antibody that inhibits EGFR signaling. In vivo testing of cetuximab has demonstrated growth inhibition and regression of chordoma. An investigator-initiated, single center, phase II study (NCT05041127) was developed to evaluate the efficacy of cetuximab for patients (pts) with advanced/metastatic chordoma. **Methods:** Eligible pts were ≥ 18 years of age, had adequate organ function, and had an ECOG performance status (PS) of ≤ 2 . Any prior line of therapy was allowed except EGFR inhibitors. A minimum of 10 pts and maximum of 29 pts were to be enrolled onto the trial based on Simon's two-stage optimal design (H_0 RR 5% vs H_1 RR 20%; one-sided $\alpha=0.05$; power=80%). Pts received cetuximab 500 mg/m² IV Q2 weeks until disease progression or unacceptable toxicity. The primary end point was response rate (RR) according to RECIST 1.1. Secondary objectives included safety/tolerability and survival metrics. Efficacy was assessed in the modified intention-to-treat (mITT) population (≥ 1 dose; ≥ 1 post-baseline scan). Exploratory objectives included analysis of the EGFR pathway at 2 time points from research-related biopsies. Pt reported outcomes (PROs) were assessed with MDASI (general and spine) questionnaires at several time points on study. **Results:** From May 2022 to Dec 2025, 29 pts enrolled. 4 were excluded from the efficacy analysis (2 withdrawal, 1 cetuximab allergy, 1 has not completed the 1st imaging assessment). Median age was 58 years (range 21–76), 15 (58%) were men, and 24 (92%) had ECOG PS of 0 or 1. The most common primary site was skull base (46%). Tumor was classified as locally recurrent in 8 pts (31%) and metastatic in 18 pts (69%). One median line of prior systemic therapy was noted (range, 0–6). At a median follow up of 28.7 months, 12 pts (48%) had radiographic cytorreduction (any tumor reduction [ATR]), but only 2 pts (8%) had a partial response (PR). Neither PR was associated with an EGFR gene alteration. Stable disease (SD) was noted in 23 pts (92%). Preliminary median PFS and median OS was 9.9 months (95% CI, 6.3 to 13.4) and 38.8 months (95% CI, 18.6 to NR), respectively. Significantly longer PFS was observed in SD-ATR (log-rank $p=0.038$), with median of 14.2 months in SD-ATR versus 9.6 months in SD without tumor reduction. 7/26 pts (27%) experienced a grade 3 cetuximab-related adverse event (AE), the most common being rash in 4 pts (15%). No grade 5 AE related to cetuximab was reported. Dose reduction occurred in 2 pts (8%). 4 pts (15%) discontinued the study due to toxicity. 4 pts remain on study. **Conclusions:** Although the primary end point has not been reached, 2 PRs are noted, and pts with SD-ATR have a longer PFS. Translational and PRO analysis are ongoing to better define biological predictors of cetuximab activity in chordoma. Clinical trial information: NCT05041127. Research Sponsor: Chordoma Foundation; Eli Lilly.

Genomic characterization of conventional, dedifferentiated, and mesenchymal chondrosarcoma: A 550-patient multicenter analysis.

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Background: The rarity of chondrosarcoma has historically impeded efforts and systematic genomic characterization. However, large, standardized, multi-center databases, such as the AACR Project GENIE, along with other, independent studies, have enabled genetic profiling of hundreds of patients with these cancers. **Methods:** The following datasets were accessed through cBioPortal: the GENIE Cohort v18.0; msk_impact_2017; metastatic_solid_tumors_mich_2017; pog570_bcgsc_2020; msk_ch_2020; msk_ch_ped_2021; sarcoma_msk_2022; sarcoma_mskcc_2022; mixed_kunga_msk_2022; msk_ctdna_vte_2024; and sarcoma_ucla_2024. These datasets included 550 unique patients: 453 conventional chondrosarcoma (CHS), 42 dedifferentiated chondrosarcoma (DDCHS), and 55 mesenchymal chondrosarcoma (MCHS). Mutational and structural variant data were also extracted from each data set and ranked by frequency. This ranked list of genes was then analyzed using g:Profiler enrichment analysis software. Dunn's test with Benjamini-Hochberg correction following Kruskal-Wallis test was performed for statistical analysis. **Results:** The average age at biopsy was 52 for CHS, 63 for DDCHS, and 32 for MCHS. DDCHS displayed the greatest genomic instability, with significantly elevated mutation count and tumor mutation burden (TMB) compared to CHS and MCHS ($p < 0.001$). Despite the higher TMB in DDCHS, the most frequently mutated genes were highly conserved between CHS and DDCHS, with six of the 20 most frequently mutated genes being shared between them. In contrast, MCHS shared only two of the 20 most frequently mutated genes with CHS and DDCHS. *TP53*, *IDH1* and -2, and *TERT* were frequently mutated in both CHS and DDCHS. Enrichment analysis indicated that DNA repair pathways were among the most frequently altered in both diseases. These pathways, while still perturbed in MCHS, appeared less prominently, with genes involved in chromatin organization being frequently mutated. Moreover, Enrichment analysis of structurally variant genes in CHS also showed frequent alterations in chromatin organizing genes, along with genes involved in NOTCH signaling. While structural variant genes were not reported with enough frequency in DDCHS and MCHS to permit the analysis, the HEY1-NCOA2 fusion product was frequently detected in MCHS. **Conclusions:** The results of this multi-institutional bioinformatics survey confirms established observations that *IDH1* and -2 mutations are the most common genetic alterations in CHS following *TP53*. DDCHS bears a similar but more advanced mutational signature with greater genomic instability. MCHS harbors a distinct mutational profile defined by the characteristic HEY1-NCOA2 fusion. Despite these differences, all three subtypes share enrichment in mutations affecting genomic integrity pathways, suggesting this as a common feature of chondrosarcoma biology. Research Sponsor: None.

Low-dose apatinib combination with first-line chemotherapy rechallenge in advanced osteosarcoma: A single-center ambispective cohort study.

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Background: First-line treatment for osteosarcoma includes various combinations of four agents: high-dose methotrexate (HD-MTX), doxorubicin (DOX), cisplatin (DDP), and ifosfamide (IFO), achieving overall efficacy rate of 41-77% and remaining the most effective systemic therapy to date. However, patients (pts) with progression after first-line therapy lack a defined second-line standard, available treatments yield objective response rate (ORR) <20% with 5-year survival <10%. Though anti-angiogenic tyrosine kinase inhibitors have limited monotherapy efficacy, preclinical studies show they enhance intratumoral drug delivery and reverse multidrug resistance, thereby synergizing with chemotherapy. Thus, apatinib, a highly selective VEGFR-2 inhibitor, was added to the previously failed first-line chemotherapy-the most effective systemic therapy-to investigate whether it could reverse chemoresistance and restore response to the original regimen. **Methods:** This ambispective cohort study enrolled pts with advanced osteosarcoma who had tumor progression after first-line chemotherapy with HD-MTX, DOX, DDP and IFO at our center. Subsequently, low-dose apatinib (250 mg/d) was administered in combination with the same four-drug chemotherapy regimen. The primary endpoint was the ORR. Secondary endpoints included disease control rate (DCR), median progression-free survival (PFS), median overall survival (OS) and adverse events (AEs). **Results:** From Jan 2018 to Jul 2025, 37 pts were enrolled, with 9 in the retrospective cohort and 28 in the prospective cohort. Of these, 27 (73%) were male and 10 (27%) were female, with a median age of 21 years (range: 10-67). 36 pts were diagnosed as conventional osteosarcoma (96.9%). Primary tumors were located in the femur (21, 56.8%), tibia and humerus (8, 21.6%), pelvis (6, 16.2%), clavicle and rib (2, 5.4%). Metastatic disease was present in 29 pts (78.4%). The most common sites of metastasis were the lung (28, 78.1%) and bone (6, 18.8%). Partial remission was seen in 8 pts, and stable disease in 23 (ORR: 21.6%, DCR: 83.8%). After a median follow-up of 17 months (mos), PFS was 5.8 mos (2.5-9.1), OS was 14.5 mos (10.3-18.7). Pts with lactate dehydrogenase <245 U/L had superior PFS (7.2 vs 3.3 mos; HR=0.28, 0.1-0.8, P=0.01), with a trend of OS benefit (14.5 vs 11.6 mos, P=0.74). Pts with alkaline phosphatase <150 U/L had a trend of PFS benefit (6.3 vs 5.8 mos, P=0.7) and significant better OS (20.3 vs 11.7 mos; HR=0.41, 0.17-1.01, P=0.046). Prognosis was not associated with gender, age, primary site, stage or first-line therapy response. AEs were consistent with known safety profiles and manageable. **Conclusions:** Low-dose apatinib combined with previously resistant first-line chemotherapy showed promising efficacy, providing a feasible therapeutic strategy for osteosarcoma pts lacking effective second-line choices. Research Sponsor: Chen Xiao-Ping Foundation for the Development of Science and Technology of Hubei Province.

First-in-human dose escalation trial of an engineered salmonella delivering L-methioninase in advanced bone and soft tissue sarcomas.

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Background: Advanced bone and soft-tissue sarcomas have limited treatment options. Tumor-selective methionine dependency is a known metabolic vulnerability. SGN1 is designed to deplete methionine locally within tumors via intratumoral colonization of an attenuated *Salmonella* vector expressing L-methioninase. Preclinical studies have demonstrated safety and targeted antitumor activity. Here, we report the results from the escalation and expansion phases of the Phase I study in patients (pts) with advanced bone and soft-tissue sarcomas. **Methods:** The Phase I study includes a dose-escalation phase where pts received intravenous (IV) (2.0×10^8 to 4.0×10^8 CFU) or intra-arterial (IA) infusion (2.0×10^8 to 6.0×10^8 CFU) once a week (QW) in 28-day cycles, followed by an expansion phase with the putative recommended Phase 2 dose (RP2D) (2.0×10^8 CFU for IV or 6.0×10^8 CFU for IA QW) in 6 cohorts, including pts with recurrent either bone or soft tissue sarcoma after at least 2 lines of chemo therapies. SGN1 was administered in combination with physician's choice systemic therapy. Administration of SGN1 was via one of three routes: IV, IA, or a combined IV/IA regimen. Efficacy was assessed by RECIST version 1.1. **Results:** At the cut-off of Aug 19, 2024, 25 pts with advanced bone and soft-tissue sarcomas were enrolled in the escalation and expansion phases (median follow-up of 5.6 months; range, 0.5–18.2), including pts with bone sarcoma (n=10) and soft tissue sarcoma (n=15). Treatment was administered via IV (n=13), IA (n=8), or a combined IV/IA (n=4) route. The disease control rate (DCR) was 76.0% (95% CI: 56.5, 93.0) in all, 70.0% (95% CI: 34.8, 93.3) in bone sarcoma, 80.0% (95% CI: 52.0, 95.6) in soft tissue sarcoma pts, and 69.2% (95% CI: 38.5, 90.9) in IV, 75.0% (95% CI: 34.8, 93.3) in IA, 100% in combined IV/IA route. Quantitative PCR analysis confirmed significant intra-tumoral colonization by SGN1 post-treatment. The median progression-free survival (mPFS) was 11.5 months (95% CI: 11.1, NE) in all, 11.1 months (95% CI: 1.1, NE) in bone sarcoma, not reached (NR) (95% CI: 3.2, NE) in soft tissue sarcoma pts, and NR (95% CI: 2.7, NE) in IV, 11.5 months (95% CI: 1.3, NE) in IA, NR (95% CI: 11.1, NE) in combined IV/IA route. Complete tumor necrosis was observed in at least two soft tissue sarcoma patients. In all pts, the most frequent treatment-related adverse events (TRAEs) were pyrexia (32.0%) and elevation of blood LDH increased (20.0%). No TRAEs leading to temporary drug discontinuation, no serious TRAEs resulting in withdrawal from the study, and no treatment-related deaths occurred. **Conclusions:** SGN1 exhibits a manageable safety profile, and showed encouraging clinical benefit in advanced bone and soft-tissue sarcoma, as evidenced by mPFS and DCR. The promising data from this phase I study supports further testing of SGN1 in Phase II studies. Clinical trial information: ChiCTR2400085361. Research Sponsor: None.

Efficacy and safety of DR4/DR5 agonist aponermin monotherapy in advanced chondrosarcoma: Preliminary report from a prospective, multicenter study.

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Background: Reported median progression-free survival (mPFS) of Chondrosarcoma is less than 4 months for patients receiving first-line systemic therapy. Aponermin, a recombinant circularly permuted human Tumor Necrosis Factor-Related Apoptosis-Inducing Ligand (TRAIL), induces tumor cell apoptosis by activating the extrinsic apoptotic pathway. This study aimed to evaluate the efficacy of Aponermin in patients with advanced chondrosarcoma.

Methods: This prospective, multicenter, single-arm study (Registration No: ChiCTR2500104488) was approved by an independent ethics committee. The planned enrollment was 32 patients aged 18-75 years with histologically confirmed advanced chondrosarcoma, documented evidence of disease progression within 6 months prior to enrollment, ECOG performance status ≤ 2 , and measurable disease per RECIST 1.1. Patients received intravenous Aponermin 10 mg/kg (days 1-5, every 14 days as one cycle) until disease progression, unacceptable toxicity, or investigator's decision to discontinue. The primary endpoint was objective response rate (ORR). Secondary endpoints included 4-month PFS rate, disease control rate (DCR), overall survival (OS), and safety. **Results:** As of January 23, 2026, 21 patients were enrolled and treated. Median age was 51 years (range: 26-70), with a median of 2 prior surgeries (range: 1-6). Eight patients had received prior drug therapy. Histopathological subtypes included: conventional grade 1, 19% (4/21); conventional grade 2, 47.6% (10/21); conventional grade 3, 4.8% (1/21); mesenchymal, 9.5% (2/21); and one case each (4.8%) of myxoid, dedifferentiated, clear cell, and unknown subtype. Twenty patients were evaluable for efficacy. Median treatment duration was 3.6 months (range: 0.5-14.0), with 4 patients still on treatment. Although no objective responses were observed, 80.0% (16/20) of DCR was achieved. Median PFS was 4.2 months (95% CI: 2.9-5.5), and the 4-month PFS rate was 57.9%. Median OS was not reached. Notably, Among patients achieving DCR, 50% maintained clinical benefit for over 4 months, including one patient with conventional grade 3 chondrosarcoma with SD lasting 7.4 months, two patients with conventional grade 2 with SD exceeding 10.0 months, and one patient with clear cell subtype with SD lasting 14 months. Aponermin demonstrated a favorable safety profile. Treatment-related adverse events occurred in approximately 9.5% (2/21) of patients, including one case (4.8%) of grade 1 allergic reaction and one case (4.8%) of hand-foot syndrome, both alleviated with symptomatic treatment. **Conclusions:** Aponermin monotherapy demonstrated promising disease control and a favorable safety and tolerability profile in advanced chondrosarcoma. Given the limited sample size and ongoing enrollment, final efficacy and safety assessments await study completion. Clinical trial information: ChiCTR2500104488. Research Sponsor: None.

Benefit of adjuvant therapy in high-risk GIST: A large-scale real-world analysis of 2,166 patients (DEEPSARC study).

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Background: Real-life data on the impact of adjuvant treatment in GIST pts are limited.

Methods: We conducted a retrospective study (Deepsarc) merging data from the NETSARC+ dataset of the French Sarcoma Group with the exhaustive health data from the national social security system (SNDS). Eligible pts were treated between January 1, 2012, and December 31, 2017 with localized GIST. The relation between overall survival (OS) and adjuvant therapy was studied univariate and multivariate, using different methods to address confounding factors.

Results: A total of 2166 GIST pts were included, with a median age of 68.0 years (interquartile range (IQR): 58.0, 76.0), a sex ratio of 1.01. The two most common primary sites were gastric (1301, 60%) and small intestine (527, 24%). Median tumor size at diagnosis was 5.3 cm (IQR 3.6-8.1). Median mitotic count was 3.0 (IQR 1.0-5.0). According to Miettinen/AFIP classification, 331/1026 (32%) were high-risk, 192/1026 (19%) intermediate risk, and 503/1026 (49%) very low or low risk vs 490/912 (53%) high-risk, 193/912 (21%) intermediate risk, and 229/912 (25%) very low or low risk with Joensuu classification. From 2012 to 2017, the proportion of pts receiving adjuvant therapy remained remarkably stable at around one third of all GIST, with higher use in high-risk (70%; 231/331) than intermediate-risk (43%; 83/192) and low-risk pts (6%; 32/503). Pts receiving adjuvant therapy were younger ($p<.001$), with less comorbidities ($p<.001$), larger tumor ($p<.001$), higher mitotic count ($p<.001$), higher risk according to Miettinen/AFIP ($p<0.001$), or Joensuu ($p<.001$), higher rate of R1 resection ($p=.019$) and higher rate of tumor rupture ($p=.001$). Median follow-up was 5.0 years (4.8-5.2). Overall, the 5y OS rate was 81% [79-83%]. Regardless of risk, for the entire population, 5y OS rate of those receiving adjuvant therapy was 82% [79%-85%] and for those not receiving adjuvant therapy was 81% [78%-83%]. For both prognostic classifications, in univariate analysis, adjuvant therapy was associated with improved survival only for high-risk pts. Multivariate analysis propensity-score adjusted analyses for age, sex, social deprivation index, morbidity index, and tumor size (3 categories: ≤ 5 / 5-10/ >10 cm) highlights a benefit of adjuvant therapy for high-risk pts, according to both AFIP/Miettinen or Joensuu classifications (Table). No clear benefit was observed in intermediate-risk pts. **Conclusion:** This study confirms the benefit of adjuvant therapy for high-risk pts (according to AFIP/Miettinen or Joensuu), but not for other risk groups. Research Sponsor: French National Cancer Institute (Institut National du Cancer, INCa); French Ministry of Health (Direction Générale de l'Offre de Soins, DGOS); French National Research Agency (Agence Nationale de la Recherche); [ANR-10-LABX-0061]; INCa-DGOS-INSERM; INCa-DGOS-INSERM ITMO Cancer_18003; Ligue Nationale contre le Cancer; Ligue contre le Cancer (Comité de l'Ain); the Fondation ARC; European Reference Network for Rare Adult Solid Cancers (EURACAN); [EU project 739521]; Health Data Hub (HDH).

Overall survival (risk of death) in high-risk GIST patients according to adjuvant therapy (reference = No adjuvant treatment), Deepsarc study (2012-2017), France.

Risk classification	N	1y HR*	95% CI**	P-value
Miettinen/AFIP	214	0.23	0.06 ; 0.92	0.017
Joensuu	312	0.49	0.24 ; 0.98	0.029

*HR = Hazard Ratio, **CI = Confidence Interval.

Standard-dose ripretinib plus sunitinib versus ripretinib dose escalation in advanced GIST after progression on four prior therapies: Preliminary results of a multicenter cohort study.

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Background: Patients with advanced GIST who progress after four lines of therapy, including imatinib, sunitinib, regorafenib, and ripretinib, face limited treatment options. Ripretinib dose escalation is a potential option recommended by NCCN and CSCO guidelines, while combination therapy with TKIs targeting complementary pathways may offer an alternative for patients harboring multiple resistance mutations. This study aims to evaluate the efficacy of ripretinib dose escalation versus combination therapy following progression on standard-dose ripretinib to identify more effective treatment strategies. **Methods:** This study is a multicenter cohort study designed to evaluate the efficacy and safety of ripretinib dose escalation versus combination therapy with sunitinib in patients with advanced GIST who have progressed after four prior lines of therapy. Eligible patients receive ripretinib dose escalation group (150 mg twice daily) or the combination therapy group (ripretinib 150 mg once daily plus sunitinib 25 mg once daily). The primary endpoint was progression-free survival (PFS). **Results:** Between September 2023 and December 2025, 30 patients were enrolled (16 in the ripretinib dose escalation group and 14 in the combination group). Primary KIT11 mutation were identified in 17 patients, 62.5%(10/16) in the dose escalation group and 50% (7/14) in the combination group, while KIT 9 mutations were 2 patients both in the combination group. As of December 30, 2025, 5 patients in the ripretinib dose escalation group remained on treatment with stable disease, whereas all patients in the combination group had experienced disease progression; 3 of these showed slow progression and continued therapy. mPFS1 with standard-dose ripretinib was comparable between groups (6.0 months [95% CI: 4.7–7.3] vs. 7.0 months [95% CI: 5.2–8.8]). Following progression, ripretinib dose escalation achieved a mPFS2 of 8.3 months (95% CI: 4.7–12.0), significantly longer than combination therapy (3.1 months [95% CI: 2.0–4.3]). OS data remain immature. Ripretinib dose escalation demonstrated better tolerability, with no grade ≥ 3 adverse events reported. In contrast, the combination group experienced higher toxicity, 35.7% discontinued treatment due to severe adverse reactions. **Conclusions:** Preliminary results indicate that ripretinib dose escalation demonstrated superior efficacy and a more favorable safety profile compared with combination therapy involving sunitinib. These findings support ripretinib dose escalation as the preferred treatment option for patients with advanced GIST who have progressed after four lines of standard therapy. However, the sample size in this study is still small, and further research with a larger sample is needed to validate this conclusion. Research Sponsor: None.

Oncologic equivalence of brand-name vs generic imatinib in neoadjuvant *KIT* exon 11 GIST: A real-world international cohort study.

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Background: Neoadjuvant imatinib is routinely used to facilitate resection of localized gastrointestinal stromal tumors (GIST) with *KIT* exon 11 mutations. However, whether generic formulations achieve oncologic outcomes equivalent to the brand-name drug in curative-intent neoadjuvant therapy remains unknown. **Methods:** We performed a retrospective, international dual-institution cohort study of 131 patients with localized *KIT* exon 11-mutant GIST treated with neoadjuvant imatinib followed by surgical resection (2010–2025) at UC San Diego and Fondazione IRCCS Istituto Nazionale dei Tumori (Milan). Patients received either brand-name or generic imatinib based on institutional practice. The primary endpoint was tumor size reduction. Secondary endpoints included histopathologic response and overall survival. Multivariable regression and Kaplan–Meier analyses were performed. **Results:** Of 131 patients, 71 (54%) received brand-name and 60 (46%) received generic imatinib. Objective response ($\geq 30\%$ tumor reduction) occurred in 54% vs 37%, respectively ($P=0.078$). Median tumor size reduction was -33.3% with brand-name and -25.5% with generic imatinib ($P=0.105$). In multivariable analysis, longer neoadjuvant duration was independently associated with greater tumor reduction ($\beta=-0.02$ per day; 95% CI, -0.04 to -0.00 ; $P=0.04$), whereas imatinib formulation, dose, and treatment center were not. Pathologic outcomes, including viable tumor percentage ($P=0.053$), necrosis ($P=0.777$), and mitotic index ($P=0.889$), were similar between groups. Five-year overall survival was 87.2% with no difference by formulation (log-rank $P=0.24$). **Conclusions:** In this first international analysis of neoadjuvant therapy for *KIT* exon 11-mutant GIST, generic imatinib demonstrated oncologic equivalence to the brand-name formulation across tumor response, pathologic, and survival outcomes. As generic imatinib use has expanded globally following patent expiration, these findings reinforce its role as a clinically effective, cost-efficient, and accessible therapy. Demonstrating therapeutic equivalence in the neoadjuvant setting has direct implications for practice guidelines, formulary decisions, and equitable delivery of precision oncology worldwide. Research Sponsor: U.S. National Institutes of Health; T32 CA121398; U01 CA278470; R01 CA292590; P30 CA023100; GIST Research Fund #3661; Jon Strong; 3661.

Tumor size reduction and objective response by imatinib formulation.			
Outcome	Brand-name (n=71)	Generic (n=60)	P Value
$\geq 30\%$ tumor size reduction	38 (53.5%)	22 (36.7%)	0.078
Any tumor size reduction	59 (83.1%)	49 (81.7%)	1.0
$\geq 20\%$ tumor size increase	5 (7.0%)	2 (3.3%)	0.452
Tumor size reduction, (median [IQR])	-33.3% (-45 to -18.4)	-25.5% (-38.8 to -10.5)	0.11

Note: P values calculated using Fisher’s exact test for categorical outcomes and Mann–Whitney U test for continuous variables. Tumor size reduction reported as median (interquartile range, IQR).

Artificial intelligence–based predictive models for recurrence and recurrence-free survival in gastrointestinal stromal tumors: A contemporary systematic review.

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Background: Recurrence after complete resection of GISTs is still a major contributing factor to long-term survival. Traditional stratification models for risk depend on clinicopathologic variables and have limited precision. Recent improvements in artificial intelligence (AI), such as machine learning (ML), deep learning (DL), and multimodal methodologies, might enhance personalized prediction of recurrence and recurrence-free survival (RFS). We performed a contemporary systematic review to evaluate the performance and clinical utility of AI-based prognostic models in resected GIST. **Methods:** PRISMA 2020 guidelines were followed for conducting a systematic review. PubMed, Scopus, and Web of Science were analyzed to search published studies published during 2019–2025 that evaluated AI-, ML-, or DL-based models predicting recurrence or RFS following complete surgical resection of localized primary GISTs. Eligible studies included retrospective or multicenter cohorts with radiologic, histopathologic, genomic, or multimodal data. Data extracted included model type, input modalities, validation strategy, and performance metrics (area under the curve [AUC] and concordance index [C-index]). **Results:** Eight studies encompassing approximately 4,000 patients met inclusion criteria. Both deep learning and multimodal fusion models showed the highest prognostic accuracy (C-index values 0.86–0.96, AUC up to 0.995). Radiomics based ML models using CT, MRI, or ultrasound yielded AUCs between 0.85 and 0.92 which were consistently superior to traditional clinicopathologic methodologies. Genomic ML models fine-tuned recurrence risk stratification beyond conventional benchmarks into molecularly distinct prognostic subgroups. DL-based histopathology estimators both predicted for RFS and for key driver mutations (KIT, PDGFRA) by bridging morphologic and molecular features. External validation cohorts showed stable performance (AUC 0.87–0.96), with calibration and decision curve analyses supporting clinical utility. **Conclusions:** AI-based predictive models demonstrate strong and reproducible performance for recurrence and RFS prediction following GIST resection, consistently outperforming traditional risk stratification systems. Multimodal and deep learning approaches integrating radiologic, pathologic, and genomic data appear most promising for precision prognostication and personalized adjuvant therapy selection. Prospective validation and explainable AI integration are needed prior to routine clinical adoption. Research Sponsor: None.

Ripretinib as preoperative therapy in patients with potentially resectable advanced gastrointestinal stromal tumors after imatinib failure: Final analysis of a prospective, multicenter study.

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Background: Cytoreductive surgery may improve outcomes in patients with locally advanced or metastatic gastrointestinal stromal tumors (GIST) after progression on imatinib. Ripretinib has shown a high objective response rate (ORR) and a favorable safety profile in advanced GIST, suggesting its potential for tumor downstaging and enabling surgical intervention. This study evaluated the efficacy and safety of ripretinib as preoperative therapy in patients with imatinib-resistant, potentially resectable advanced GIST. **Methods:** This single-arm, multicenter, exploratory study (NCT05132738) enrolled patients with imatinib-resistant, locally advanced or recurrent metastatic GIST who met the following criteria: 1) ≤ 5 evaluable lesions on CT/MRI; 2) resection deemed high-risk by multidisciplinary team (MDT) assessment (meeting one of the following): a) The maximum diameter of a single lesion is ≥ 10 cm; b) Organ function damage surgery is required; c) Multiple organ resection surgery is required. Patients received ripretinib 150 mg once daily (QD) up to 6 months before surgery. The primary endpoint was the no evidence of disease rate (NED Rate). Secondary endpoints included the R0/R1 resection rate, surgery rate, and ORR. **Results:** As of January 2026, 20 patients were enrolled, with a median age of 58 years (range: 31–74). The most common primary tumor site was the small intestine (70%). The median sum of target lesion diameters was 10.8 cm (range: 3.2–33.7). The median duration of preoperative ripretinib was 5 months (range: 2–6). The median best percentage change in the sum of target lesion diameters was -20.5% (range: -47.2% to +56.0%). 8 patients (40.0%) achieved a partial response (PR) and 10 patients (50.0%) had stable disease (SD). Median time to response was 2.0 months (range: 2.0–6.0). 70% (14/20) of patients underwent surgery and the NED rate was 92.9% (13/14). Of the 13 patients who achieved R0 resection, 8 (61.5%) have maintained NED to date. Only 1 patient experienced intestinal fistula as a surgical complication, which was unrelated to ripretinib treatment. After surgery, 6 patients continued ripretinib therapy, while 3 switched to imatinib therapy and 5 switched to sunitinib therapy. With a median follow-up of 20.4 months (range: 8.1–47.6), the median overall survival (OS) was immature. **Conclusions:** These findings demonstrate that preoperative ripretinib effectively reduced tumor burden in patients with imatinib-resistant, potentially resectable advanced GIST, and facilitated successful surgery intervention. Notably, the approach achieved a high NED rate and a low surgical complication rate, supporting ripretinib as a safe and effective preoperative treatment option. Clinical trial information: NCT05132738. Research Sponsor: None.

Clinical characteristics and outcomes of germline and sporadic NF1-associated gastrointestinal stromal tumors: Insights from a real-world patient registry.

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Background: Neurofibromatosis type 1 (NF1)-associated gastrointestinal stromal tumor (GIST) is a rare, distinct molecular subtype, typically lacking KIT or PDGFRA mutations. Standard KIT-targeted therapies show limited efficacy, highlighting the need for alternative systemic approaches. Real-world data on the clinical features, treatment patterns, and outcomes of NF1-associated GIST are limited. **Methods:** The Life Raft Group (est. 2000) Registry is an international, observational registry. Patients with GIST and documented NF1 mutations without another primary oncogenic alteration were included. Demographic, tumor, and treatment characteristics were summarized; group differences were assessed using Fisher's exact test, and disease-free survival (DFS) and overall survival (OS) were estimated by Kaplan-Meier methods. **Results:** A total of 38 patients were identified (1.3% of the total registry, n = 2990) and stratified as germline NF1 (n = 18) and sporadic NF1 (n = 20). Median age at diagnosis was 57 years; 53% (n = 20) of patients were female, with a higher proportion of germline NF1 than sporadic NF1 (60%, n = 12 vs 40%, n = 8). Conversely, among males, sporadic NF1 was more common than germline NF1 (67%, n = 12 vs 33%, n = 6). Tumors predominantly arose in the small bowel (79%). Germline NF1 patients exhibited significantly higher rates of multifocal disease compared with sporadic NF1 patients (85% vs 15%, p = 0.0006). Most patients presented with localized disease (84%, n = 32), with similar proportions between germline and sporadic NF1 (78%, n = 14 vs 90%, n = 18). All localized patients underwent surgical resection, achieving R0 margins in 72% of cases. Among patients who developed advanced disease (de novo metastatic or recurrent disease; n = 18), 67% received systemic therapy including MEK inhibitors in 22% (n = 4). One patient achieved durable disease control on selumetinib for nearly six years and remains on treatment. Median follow-up was 37.6 months (2.5–185). In localized patients, 5-year DFS was 65% (95% CI: 39–100) for germline and 46% (95% CI: 25–84) for sporadic NF1; median DFS was 55.4 months in sporadic NF1 and not reached in germline NF1. 10-year OS was 78% (95% CI: 62–98) overall, 88% (95% CI: 67–100) for germline, and 83% (95% CI: 64–100) for sporadic localized patients. Survival estimates in metastatic patients were highly variable due to small numbers. **Conclusions:** In this real-world registry analysis, NF1-associated GIST shows small bowel predominance and frequent multifocality, particularly in germline NF1. Most patients achieve disease control with surgery. MEK inhibitors may demonstrate potential activity in advanced NF1 GIST. These findings highlight phenotypic differences between germline and sporadic NF1-associated GIST and support further evaluation of MEK-targeted therapy in patients with metastatic disease. Research Sponsor: None.

Updated clinical and translational results of olverembatinib (HQP1351) in patients with succinate dehydrogenase (SDH)–deficient tumors.

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Background: SDH deficiency causes succinate accumulation and metabolic defects in gastro-intestinal stromal tumor (GIST) and paraganglioma. Olverembatinib downregulates lipid uptake protein CD36, restricting fatty acid supply required for SDH-deficient GIST cell growth. We report updated clinical and translational results from study HQP1351SJ0003 (NCT03594422) of olverembatinib in SDH-deficient GIST and paraganglioma. **Methods:** Patients (pts) (≥ 12 years) with GIST and other solid tumors received olverembatinib 30 to 50 mg PO QOD. Primary cells from tumor tissues of 9 pts with SDH-deficient GISTs were used for *ex vivo* analyses. All samples were collected at Sun Yat-sen University Cancer Center, with informed consent from pts. Cell migration/invasion was evaluated by wound healing, Transwell migration, and Matrigel invasion assays. Lipid levels were quantitated by LC-MS. Knockdown of CD36 and p38 was done by siRNA. Protein levels were assessed by western blot. **Results:** As of November 13, 2025, a total of 32 pts, including 26 pts with IHC-confirmed SDH-deficient GIST, had received olverembatinib. The median age of pts with SDH-deficient GIST was 30 (range 13–56) years; 19 (73.1%) were female. Twenty-five pts (96.2%) had received ≥ 1 TKI and 13 (50.0%) ≥ 3 . Six (23.1%) pts experienced PR as best response, and the median PFS was 25.7 (range 12.9–NR) months. An additional six pts with paraganglioma had received olverembatinib (all were SDH-deficient as determined by either negative SDHB IHC or *SDHB* gene mutation). The median age was 47.5 (range 31–61) years; all were male. Best responses were observed in four pts, with SD lasting ≥ 4 cycles (CBR, 66.7%); SD represents meaningful clinical benefit in this slow-growing tumor type. The median PFS was 8.25 (range 1.87–NR) months. SDH-deficiency was associated with a higher risk of tumor metastasis. In SDH-deficient (vs. SDH-competent) GIST cells, significantly higher linoleic acid levels were observed. Supplementation of free fatty acids promoted SDH-deficient cell migration, which could be inhibited by olverembatinib at 30 nM. In addition, siRNA knockdown of p38, a kinase target of olverembatinib, and treatment with two p38 inhibitors significantly downregulated CD36 protein levels, suggesting that p38 regulates cellular CD36. Further, western blot analysis showed that olverembatinib dose-dependently inhibited CD36 protein and phosphorylated p38 protein levels in primary cells from SDH-deficient pts. These findings suggest olverembatinib suppresses fatty acid-promoted migration via the p38-CD36 pathway. **Conclusions:** Olverembatinib showed sustained clinical efficacy in SDH-deficient GIST and paraganglioma. Mechanistically, olverembatinib inhibits fatty acid-promoted invasion and migration of SDH-deficient GIST by targeting the p38-CD36 signaling pathway. Clinical trial information: NCT03594422. Research Sponsor: Ascentage Pharma Group Corp Ltd. (Hong Kong).

Circulating tumor DNA monitoring for early detection of disease recurrence in bone/soft tissue sarcoma.

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Background: Circulating tumor DNA (ctDNA) is a powerful, minimally invasive biomarker of treatment response and patient prognosis in many tumors. Here, we assessed the clinical performance of the Signatera assay in patients with bone and soft tissue sarcomas in assessing molecular residual disease (MRD). **Methods:** We performed a retrospective analysis of patients at our institution who underwent commercial ctDNA testing using the Signatera mPCR-NGS assays after curative intent resection of their primary tumor. Patients with oligometastatic disease were included if they also underwent resection of oligometastatic sites and did not have any evidence of residual disease. Additional inclusion criteria included three or more ctDNA draws in the MRD setting with at least one ctDNA blood collection within one of year of completing curative intent procedures and at least 6 months of clinical follow up after surgery. ctDNA positivity was defined as any detectable level of ctDNA at any time point in the patient's treatment course after surgery. **Results:** We reviewed 305 patients who underwent Signatera ctDNA collection; 107 patients met the inclusion criteria for this study. The most common reason for not meeting inclusion criteria was advanced/unresectable disease (n = 168). The included 107 patients underwent over 1300 plasma ctDNA assessments in the MRD setting (average 12 ctDNA assessments per patient) between September 2019 and November 2025. For the overall cohort, sensitivity was 75% (36/48); specificity was 100% (36/36). One patient with angiosarcoma had ctDNA detected one month prior to data cut-off and was awaiting re-staging imaging. The largest represented histologies were leiomyosarcoma (n = 42) and undifferentiated pleomorphic sarcoma and related tumors (n = 22); sensitivity were 85% (22/26) and 57% (4/7), respectively. The median duration of follow-up after surgery was 41 months (range 1.6 to 79 months). Of the 48 patients with disease recurrence, 27 (60%) developed local disease recurrence only, 17 (38%) developed distant recurrence only, and 4 (9%) developed local and distant disease recurrence. The most common site of distant disease recurrence was in the lungs (n = 16). Sensitivity was lowest in the patients who developed disease recurrence isolated to the lungs (42%, 5 out of 12) compared to patients who developed disease recurrence not confined to the lungs (89%, 32 out of 36). Of the patients who had ctDNA detected at time of recurrence, 47% (17/36) demonstrated ctDNA positivity before detection of recurrence on imaging with an average lead time of 20 days. **Conclusions:** In a cohort of over 100 sarcoma patients with over 1300 plasma samples collected in the MRD setting, Signatera ctDNA assay demonstrated a clinical sensitivity of 75% and specificity of 100% for relapse detection with the highest sensitivity in leiomyosarcoma (85%) and when disease recurrence was not confined to the lungs (89%). Research Sponsor: None.

Cell proliferation, immune cell infiltration, and survival outcomes in sarcomas with high cancer-associated fibroblast expression.

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Background: Cancer-associated fibroblasts (CAFs) play an integral role in the tumor micro-environment and have been linked to tumor aggravation and promotion of metastatic potential. CAFs are often abundant in sarcomas, but their role is understudied partly because both share a similar mesenchymal origin. We aimed to investigate the relationship between CAFs and clinical characteristics in sarcomas using transcriptomics. **Methods:** Genomic and clinicopathologic data was acquired from The Cancer Genome Atlas Sarcoma cohort. Cases were divided into high and low CAF groups using the median CAF level. Immune cell compositions including CAFs were determined using the xCell algorithm. Institutional Review Board waiver was deemed applicable as the data is de-identified from publicly available databases. **Results:** A total of 258 patients including leiomyosarcoma (LMS, n=83), myxofibrosarcoma/undifferentiated pleomorphic sarcoma (MFS/UPS, n=80), dedifferentiated liposarcoma (DDLPS, n=46), and other pathologies (n=20), were analyzed. DDLPS had significantly greater CAFs than the other subtypes ($p=0.0025$). CAF expression varied significantly by tumor grade, with grade 3 tumors having the lowest CAF expression and grade 1 & 2 tumors having significantly higher CAF expression ($p<0.001$). Ki67 was significantly lower in the high CAF tumors ($p<0.001$). On GSEA, high CAF sarcomas showed significantly less enrichment in myc targets v1 (NES= -2.67, FDR<0.001), myc targets v2 (NES=-2.25, FDR<0.001), G2M checkpoint (NES=2.39, NES<0.001), E2F targets (NES=-2.66, FDR<0.001), mitotic spindle (NES= -1.33, FDR= 0.015), and mTORC1 signaling (NES=-2.33, FDR <0.001); all consistently showing that high CAF sarcomas are less proliferative. In terms of genomic instability, high CAF sarcomas were significantly associated with less homologous recombination deficiency ($p<0.001$), intra-tumor heterogeneity ($p<0.001$), aneuploidy ($p=0.003$), and silent mutation rates ($p=0.036$). Analysis of immune cell composition revealed significantly less infiltration of B-cells ($p=0.004$), CD8 T-cells ($p=0.013$), Th1 cells ($p<0.001$), Th2 cells ($p=0.008$), and macrophages ($p=0.027$) in the high CAF group. Differential gene expression analysis demonstrated that C7, SESN1, FAM198A, were the most, and WNT7B, ENO1, TM4SF19 were the least expressed among 20511 genes analyzed in high CAF sarcomas. High CAF sarcoma were associated with significantly better disease-free survival (HR= 0.48 (95% CI 0.34-0.68), $p<0.001$) as well as overall survival compared with low CAF sarcomas (HR= 0.5 (95% CI 0.34-0.76), $p<0.001$). **Conclusions:** CAFs are associated with less cell proliferation, less immune cell infiltration, and better survival. Further studies are warranted to develop CAFs as a prognostic biomarker for sarcoma patients. Research Sponsor: None.

Myxoid/round cell liposarcoma misdiagnosis incidence, etiology, and importance of NY-ESO-1 testing: Retrospective analysis of the Tempus database.

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Background: Liposarcoma is composed of multiple unique sarcoma subtypes, specifically myxoid/round cell liposarcoma (MRCLS), well differentiated and dedifferentiated liposarcoma (WD LPS and DD LPS), and pleomorphic liposarcoma. These are genetically distinct entities with different treatment paradigms. MRCLS is driven by a translocation between DDIT3 and FUS or EWSR1, detectable in 100% of MRCLS. WD and DD LPS are characterized by amplification of MDM2 and CDK4, and pleomorphic LPS is genetically complex. Recently, new treatments for liposarcoma are specific to the LPS type (CDK4/6 inhibitors; CTA directed engineered T Cells) which highlights the importance of an accurate liposarcoma subtype diagnosis. **Methods:** A retrospective analysis of the tempus RNA database for DDIT3 translocations and NY-ESO-1 (CTAG1B) expression in MRCLS was conducted. 101 patients (pts) with MRCLS were identified; 27 pts lacked Next Generation Sequence data for tumor samples leaving 74 pts that were selected for analysis. RNA was sequenced with either the Tempus RS or the RS.v2 assays. Patients' tumor samples with tumor purity <30% were excluded from assessment of CTAG1B expression. Gene expression values in this analysis were normalized by transcripts-per-million (TPM) transformed to $\log_2(\text{TPM}+1)$ units. The threshold of 2 ($\log_2(\text{TPM}+1)$) was set as the cut off of true positive for CTAG1B expression. **Results:** The DDIT3 fusion was identified in 65/74 (88%) patients. In 9/74 (12%) patients, there was no DDIT3 fusion detected. Out of the 65 patients that were positive for the MRCLS translocation 60/65 (92%) were DDIT3-FUS, and 5/65 (8%) were DDIT3-EWSR1. The MRCLS DDIT3 fusion-negative samples were 5/9 (56%) positive (pos) for MDM2 amplification and CDK4 amplification. The Tempus tumor of origin algorithm predicted all DDIT3 fusion-pos MRCLS samples to be soft tissue sarcoma (where predictions were made; 53 of 65 pts) and the DDIT3 fusion-neg samples to be fibrosarcoma in one case and liposarcoma in 7 cases. The last fusion-neg case did not have a tumor of origin prediction. The median expression of CTAG1B was 7.14 TPM in all patients, 7.2 TPM (range 3.1 to 8.7) in DDIT3-FUS samples, 7.5 TPM (range 5.7 to 7.7) in DDIT3-EWSR1 samples, and 0.04 (range 0.0 to 3.7) in DDIT3 fusion-neg samples. There was no difference in CTAG1B expression by biopsy site, metastatic status, stage, tumor purity, or center of diagnosis. **Conclusions:** It is of critical importance to accurately determine the liposarcoma subtype which influences the selection of new targeted treatments. This analysis highlights a 12% rate of misdiagnosis of MRCLS and suggests that WD/DD LPS can be misdiagnosed as MRCLS. Additionally, this study predicts that 100% of MRCLS with confirmed DDIT3 translocation will be NY-ESO-1 (CTAG1B) pos which highlights the utility of NY-ESO-1 as a diagnostic marker for NY-ESO-1 directed therapies. Research Sponsor: Adaptimmune; US World Meds CT, LLC.

Synovial sarcoma misdiagnosis and potential utility of NGS testing patient identification for autologous T cell therapy: Retrospective analysis of Tempus database.

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Background: Metastatic synovial sarcoma (SS) is commonly treated with anthracycline and other chemotherapy with poor survival outcomes. Apatemestrone autoleucel (Tecelra) is a genetically modified autologous T cell therapy that was FDA approved in August 2024, based on ORR of 43.2% and median DoR of 6 months. It is indicated for previously treated HLA-A*02:01-03 and 06 allele positive patients (pts) with unresectable or metastatic SS whose tumors express MAGE-A4. SS is characterized by SS18-SSX gene fusion in > 95% of cases and this gene fusion is not found in other neoplasms. Commercial NGS testing may contribute to identification of eligible pts. **Methods:** Pts with diagnosis of SS and/or SS18 gene fusion were identified by retrospective analysis of the Tempus database. Demographic and disease characteristics were described for each pt and assessed for correlation with diagnosis and presence of the SS18 gene fusion. RNA was sequenced with the Tempus RS and RS.v2 assays. Gene expression values in this analysis were normalized by transcripts-per-million (TPM) and transformed to $\log_2(\text{TPM}+1)$ units. The threshold of 1.62 ($\log_2(\text{TPM}+1)$) was set as the cut off for determining true positive of MAGEA4 expression. HLA type and RNA expression of MAGE-A4 was used to identify pts potentially eligible for associated T cell therapies. **Results:** 110 pts were analyzed, including 86 pts (78%) with SS diagnosis with SS18 fusion, 12 pts (11%) with SS diagnosis but no detected SS18 fusion (SS/SS18-), and 12 pts (11%) with SS18 fusion but a non-SS diagnosis. Age at diagnosis, sex, race, state of diagnosis, and institution type (academic vs non-academic) were not associated with misalignment between the reported diagnosis and presence or absence of the SS18 fusion. For SS/SS18- pts the location of the tumor did not differ from expected SS primary locations, and the Tempus tumor of origin predicted SS diagnosis in 2/12 pts, non-SS diagnosis in 7/12 pts, and not reported 3/12 pts. The most common predicted non-SS diagnosis was malignant peripheral nerve sheath tumor (MPNST, 5 pts). Non-SS/SS18+ pts did occur in unusual locations (Pancreas, small intestine, bone, peripheral nervous system), and 10/12 were predicted by the tempus tumor of origin algorithm to be SS. The recorded diagnosis in these 12 pts was more commonly another sarcoma subtype (10/12), rather than a non-sarcoma diagnosis (2/12). MAGE-A4 expression > 1.62 TPM was detected in 71% of all pts, 74% SS/SS18+ pt, 58% of SS/SS18- and 58% of non-SS/SS18 pts. When considering the required HLA type and MAGEA4 expression then 35% of all pts would be potentially eligible for apatim-
cel. **Conclusions:** Commercial NGS testing may increase identification of pts with SS, which is important for novel T cell therapy eligibility. A low threshold should be considered for diagnosing SS in unusual locations when the SS18 fusion is detected. Research Sponsor: adaptimmune; US World Meds CT, LLC.

Ultra-sensitive whole-genome sequencing–based molecular residual disease detection in resectable sarcoma in MONSTAR-SCREEN-3.

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Background: Circulating tumor DNA (ctDNA)–based molecular residual disease (MRD) detection has shown strong prognostic value in multiple epithelial cancers, but its utility in sarcoma remains poorly defined. Sarcomas are highly heterogeneous and often represent low-shedding tumors, limiting the sensitivity of conventional assays. The MONSTAR-SCREEN-3 evaluates the clinical performance of a whole-genome sequencing (WGS)–based MRD assay in a pan-cancer cohort, including patients with sarcoma. **Methods:** Personalized ctDNA panels were generated using a WGS-based tumor-informed platform (Myriad Genetics), incorporating up to 1,000 tumor-specific variants identified through WGS of matched tumor tissue. Serial plasma samples were collected at baseline, 1 month post-surgery, quarterly during the first year, and biannually thereafter for up to two years. **Results:** As of November 2025, 35 patients with resectable soft tissue sarcoma (n=33) and osteosarcoma (n=2) were enrolled; MRD results were available for 72 samples from 24 patients. Of whom, histology was myxofibrosarcoma (n=7), undifferentiated pleomorphic sarcoma (n=7), myxoid liposarcoma (n=5), dedifferentiated liposarcoma (n=3), epithelioid sarcoma (n=3) and others (n=10). Clinical staging distribution included Stage I/II/III/IV: 15%/19%/50%/15%. Most of patients underwent upfront radical surgery (2 cases received neoadjuvant chemotherapy). Personalized panel creation succeeded in 100% of patients (24/24), identifying a median of 3,510 highly confident tumor-specific alterations per patient (range: 730–7,931) and yielding bespoke panels containing 386–1,000 alterations. Customized panels were created with 96.4% SNVs and 3.6% indels. The assay demonstrated 87.5% baseline ctDNA detection (21/24), with 16.7% detected at ultra-sensitive levels (tumor fraction <100 parts per million [ppm]). In the ctDNA-negative cases, ctDNA tumor fractions were 0.0, 0.8 and 6.2 ppm, classified as ctDNA-negative based on a statistical threshold set at 99.615% specificity. Post-surgical MRD positivity rates were 20.0% (4/20) at 1 month, 7.1% (1/14) at 3 months, and 28.6% (2/7) at 6 months. Among these patients, four patients developed radiographic recurrence, with MRD detection preceding imaging by median 1.1 months (0.1–3.0). Extended follow-up and comprehensive longitudinal ctDNA dynamics will be presented. **Conclusions:** The WGS-based ctDNA assay demonstrated high technical feasibility in sarcoma, enabling detection of patient-specific tumor variants across a highly heterogeneous and low-shedding tumor population. In our cohort, MRD positivity was observed exclusively in patients who subsequently developed recurrence, highlighting the potential utility of WGS-based tumor-informed MRD analysis for surveillance and risk stratification in sarcoma. Clinical trial information: UMIN000053975. Research Sponsor: SCRUM-Japan Funds (<https://scrum-japan.ncc.go.jp/>); Myriad Genetics.

Identification of checkpoint inhibitor resistance mechanisms in leiomyosarcoma through enrichment of active chromatin-associated cell-free DNA.

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Background: Leiomyosarcoma (LMS) is a sarcoma subtype with poor metastatic outcomes and limited treatment options. Checkpoint inhibitors (CPI) combination therapy may benefit LMS patients (pts). We previously showed (Lopes, ASCO 2025) that a liquid biopsy assay enriching for active chromatin-associated cell-free DNA (cfDNAac) identified biomarkers predicting clinical benefit in LMS pts treated with durvalumab plus olaparib or cediranib (NCT03851614). Here, we report longitudinal cfDNAac findings at baseline and progression. **Methods:** Plasma samples at baseline (n=30) and disease progression (n=22) were analyzed using a cfDNAac capture platform. Univariate analysis and recursive feature elimination identified genomic features associated with clinical benefit rate (CBR; complete response/partial response or stable disease >6 months). Molecular transcriptomic profiles, pathway enrichment, and copy number variation (CNV) were analyzed and correlated with CBR and progression-free survival (PFS). Linear mixed-effects models assessed temporal differences in cfDNAac-derived biomarkers between CBR and non-CBR groups. **Results:** A total of 1,570 baseline cfDNAac features distinguished pts who achieved CBR from those who did not (n=8 vs 22, $p < 0.01$). Pts with CBR exhibited enrichment of immune-related signatures (i.e., B and T-cell activation, lymphocyte differentiation, and a decrement of extracellular matrix organization [ECM]), all of which were individually significantly associated with longer PFS ($p < 0.05$). Upon progression, B-cell and T-cell activation significantly decreased, whereas ECM-related signatures increased in CBR compared to non-CBR group, the latter of which remained stable. A higher baseline tumor fraction (>5%) was also associated with reduced CBR ($p < 0.05$) and shorter PFS (HR = 3.33; CI: 1.32–8.40 $p < 0.01$). Recurrent CNV losses on chromosome 15 correlated with improved PFS (HR = 2.48; 95% CI: 0.99–6.22; $p = 0.052$) and CBR ($p = 0.0073$). At progression, these CNV reverted in CBR pts but remained stable in non-CBR patients. **Conclusions:** This active chromatin-associated cell-free DNA profiling enables a non-invasive monitoring of dynamic tumor microenvironment remodeling over time and provides insights into emerging mechanisms of resistance to CPI in LMS pts. Research Sponsor: Hold'em for Life.

Prognostic biomarkers in retroperitoneal dedifferentiated liposarcoma and their clinical impact on patient management.

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Background: The prognosis of patients (pts) with retroperitoneal dedifferentiated liposarcoma (DDLPS) is mainly driven by tumor size, grade, patient age, and completeness of resection. Furthermore, the expression of myogenic markers has been associated with poorer outcomes. Prognostic nomograms, such as Sarculator, and transcriptomic signatures—most notably the Complexity INDEX in SARComas (CINSARC)—have improved risk stratification. However, given the rarity of DDLPS and the limited evidence guiding treatment, identifying robust prognostic biomarkers remains a major challenge. This study evaluated the prognostic impact of clinical, morphological, and molecular features and assessed the performance of Sarculator and CINSARC in retroperitoneal DDLPS. **Methods:** A retrospective observational study was conducted on pts with retroperitoneal DDLPS treated at the Veneto Institute of Oncology (IOV)-IRCCS between 2004 and 2024. Tumor samples with adequate material underwent morphological, immunohistochemical, and molecular analyses, including CINSARC assessment. Disease-free survival (DFS) and overall survival (OS) were evaluated in surgically treated pts (Cohort 1), while progression-free survival (PFS) and OS were assessed in pts receiving first-line chemotherapy (Cohort 2). Sarculator was applied to Cohort 1, and its discriminative ability was evaluated using ROC curves. Concordance between CINSARC and Sarculator was also examined. **Results:** A total of 119 pts were included. In the overall population, tumor grade (3 vs 2: HR, 2.23; 95% CI 1.06 – 4.70; $p = 0.03$) and age (<65 vs ≥ 65 : HR, 0.43; 95% CI 0.22 – 0.85; $p = 0.02$) were the most significant predictors of OS. In Cohort 1, these variables remained determinants of survival. In Cohort 2, sex, tumor size and differentiation significantly affected survival, with rhabdomyoblastic differentiation conferring the worst prognosis ($p = 0.04$). When Sarculator was applied to Cohort 1, a moderate discriminative ability was observed for OS (AUC = 0.75), with a lower performance for DFS (AUC = 0.64). Molecular analyses were performed on 32 samples; MYOG transcripts, indicative of rhabdomyoblastic differentiation, were detected in 8 cases. Based on CINSARC, 11 pts (34.4%) were low risk and 21 (65.6%) high risk. Agreement between Sarculator and CINSARC was moderate for both OS (Cohen's Kappa, $\kappa = 0.40$) and DFS ($\kappa = 0.55$). **Conclusions:** To our knowledge, our study is among the largest conducted in retroperitoneal DDLPS specifically evaluating clinico-pathological features and the performance of Sarculator and CINSARC. Our findings support the negative prognostic impact of rhabdomyoblastic differentiation. Further investigation of differentiation patterns, combined with prognostic nomograms and transcriptomic signatures, may improve the identification of high-risk pts and support more personalized therapeutic strategies. Research Sponsor: None.

Unsupervised clustering of RNA-Seq data to identify molecular subtypes of sarcomas.

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Background: Sarcomas are a rare and heterogeneous group of malignancies, which include over 100 histological subtypes. Their histologic diversity present significant diagnostic and therapeutic challenges. This study aimed to define clinically relevant transcriptional subtypes using RNA-Sequencing (RNA-seq) data, and to further characterize the immune and metabolic microenvironment. **Methods:** This study uses data from the “Cohort to Augment the Understanding of Sarcoma Survivorship Across the Lifespan” (CAUSAL) study, which has enrolled sarcoma patients, treated at VUMC, from 2002–2026 for investigation of health outcomes. We analyzed RNA-seq data from tumor samples of 430 participants representing 42 unique histological sarcoma subtypes. We utilized sparse K-means clustering to identify stable subtypes and developed a classifier using a 310-gene panel. The immune microenvironment was characterized by applying CIBERSORTx deconvolution. Sarcoma subtype reproducibility and prognostic validity were evaluated using the Cancer Genomic Atlas data. **Results:** Among 430 samples, consensus matrices and diminishing gains in Cumulative Distribution Function (CDF) behavior yielded six distinct sarcoma molecular subtypes (SMS), each demonstrating strong correlation with known sarcoma histologies. SMS1 (labeled as “Cytotoxic-Adaptive”, n=30) and SMS6 (“Interferon-Activated”, n=97) were characterized by robust immune infiltration and interferon signaling, suggesting a potential sensitivity to immune checkpoint blockade. SMS2 (“Myeloid-Dominant”, n=93) primarily grouped undifferentiated pleomorphic sarcoma, giant cell sarcoma, and myxofibrosarcoma, and exhibited an immune-suppressive, macrophage-rich phenotype. SMS3 (“Early-Onset”, n=58) mostly grouped Ewing and synovial sarcoma and comprised mostly fusion-driven tumors with an immune-desert landscape. SMS4 (“EMT-Stromal”, n=107) mostly comprised desmoid and leiomyosarcoma and was defined by epithelial-mesenchymal transition and fibrosis, correlating with the poorest 10-year overall survival ($p=0.022$). SMS5 (“Metabolic”, n=45) consisted exclusively of Gastrointestinal Stromal Tumors, with distinct metabolic programming and favorable prognosis. **Conclusions:** Each SMS transcends histological boundaries, grouping tumors based on shared immune, stromal, and metabolic features. This classification highlights distinct vulnerabilities in the tumor microenvironment, offering a functional framework to guide future precision treatment interventions, such as immunotherapy for SMS1/SMS6 and stromal-targeting agents for SMS4. Research Sponsor: National Cancer Institute/U.S. National Institutes of Health; 4UH3CA260318-03.

A subset analysis of clinical activity and pharmacodynamic biomarkers in patients with sarcomas in the phase 1 dose-escalation study of STC-15, a METTL3 inhibitor.

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Background: The RNA methyltransferase METTL3 is responsible for the generation of N6-methyladenosine (m6A), the most abundant modification on mRNA and long non-coding RNA. Accumulating evidence suggests numerous roles of METTL3 in cancer initiation and progression highlighting the rationale for targeting this enzyme in oncology. STC-15, a first in class small molecule inhibitor of METTL3 developed by Storm Therapeutics, demonstrated efficacy in pre-clinical models of cancer characterized by their dependence on m6A-mediated mRNA metabolism, including sarcomas that derive from a common mesenchymal progenitor. We report the clinical activity and pharmacodynamic (PD) biomarkers observed in a subset analysis of sarcomas from a first-in-human trial in patients with advanced malignancies. Full results of the study have been previously presented. **Methods:** This multi-center, open-label, dose escalation study of STC-15 administered oral capsules daily (QD) or three times a week (TIW) in 21-d treatment cycles. Dose escalation followed a 3+3 modified Fibonacci regimen. Primary objectives (safety and pharmacokinetics (PK)) and secondary objectives (efficacy) were previously presented. A subset analysis of sarcoma and selected patients evaluates anticancer activity and PD biomarkers, including target engagement, gene expression analysis, and targeted m6A RNA sequencing using the EpiPlex platform. **Results:** Of 42 patients enrolled, 35 were evaluable and 13 were sarcoma patients with a mean of 3 prior lines of therapy. Of 13 sarcoma patients with at least 1 on-treatment scan, DCR was 54% at 12 weeks with 1 confirmed PR (8% ORR) in angiosarcoma (DOR 22 months), and mPFS of 5.5 months as of 27 January 2026. Seven sarcoma patients presenting with four subtypes experienced a best response of SD, including tumor regressions. Treatment duration ranged from 15-828 days, with two sarcoma patients remaining on treatment for 590 and 828 days, respectively. An average of >50% reduction in m6A on mRNA in peripheral blood within the first 24h post dosing was observed in dose-escalating cohorts from 60 mg QD to 200 mg TIW, confirming target engagement. Moreover, we present an expanded analysis using the m6A-directed NGS EpiScout platform, where we evaluate both the effects of STC-15 on global m6A mRNA abundance and transcriptional changes that may contribute to an anti-tumor response specific to soft tissue and bone sarcomas. **Conclusions:** Treatment with STC-15 offers a new paradigm for the treatment of a broad range of sarcomas by halting the cell differentiation process from mesenchymal progenitors. Early biomarker data provide proof of mechanism in target engagement and changes in gene expression, consistent with pharmacological activity and clinical response. Further investigation of efficacy and biomarkers of STC-15 in a Phase 2 sarcoma study is ongoing. Clinical trial information: NCT05584111. Research Sponsor: None.

Use of subtype-specific patterns of clinically relevant antibody–drug conjugate targets in sarcoma to guide precision oncology strategies.

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Background: Sarcomas are rare, biologically heterogeneous malignancies with limited targeted treatment options. Antibody–drug conjugates (ADCs) have demonstrated clinical efficacy across multiple solid tumors by exploiting tumor-associated surface antigens; however, their development in sarcoma has been limited by incomplete characterization of ADC target expression across subtypes. We evaluated expression of clinically relevant ADC targets across sarcoma histologies using bulk RNA sequencing and compared these patterns to cancer types with established ADC activity to generate a sarcoma-wide map of ADC target expression. **Methods:** We analyzed expression of 18 genes encoding cell-surface ADC targets that are FDA-approved or in active clinical development across more than 1,000 sarcoma samples spanning multiple histologic subtypes. Transcriptomic data were derived from The Cancer Genome Atlas (TCGA), an institutional sarcoma registry, and the Oncology Research Information Exchange Network (ORIEN). Per-sample z-scores were generated using pan-cancer distributions to enable standardized comparison. Z-score distributions were summarized using ordinal bins to define target enrichment across sarcoma subtypes. Parallel pan-cancer analyses were performed for contextual comparison. **Results:** Sarcomas demonstrated heterogeneous but subtype-specific expression of multiple ADC targets across datasets. Several subtypes exhibited elevated expression of select ADC targets, with z-scores comparable to or exceeding those observed in tumor types where ADCs have established clinical activity. ADC targets of particular interest included LRRC15 and CD276 (B7–H3). LRRC15, currently in investigation as an ADC in breast cancer, demonstrated enrichment in sarcoma, with 28% of undifferentiated pleomorphic sarcoma and 38% of dedifferentiated liposarcoma samples exhibiting z-scores > 2, compared to 12% in breast cancer. CD276 similarly showed subtype-specific overexpression across these sarcoma subtypes. No single target was uniformly overexpressed across all sarcomas, underscoring biologic heterogeneity. Pan-cancer comparison revealed that certain sarcoma subtypes ranked among the highest expressors for specific ADC targets. **Conclusions:** Across a cohort exceeding 1,000 sarcoma patients with diverse histological subtypes, we identify subtype-specific overexpression of multiple clinically relevant ADC targets. This subtype expression map provides a biologic rationale for expanding ADC development into molecularly selected sarcoma subpopulations and supports biomarker-enriched approaches to ADC trial design. Ongoing studies will validate these findings at the protein level using a sarcoma surfaceome approach, including immunohistochemistry and mass spectrometry based profiling. Research Sponsor: None.

Distinct prognostic roles of *IDH* mutation and high-risk genomic alterations in patients with primary chondrosarcoma.

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Background: Prior studies report mixed associations between *IDH* mutation and survival in chondrosarcoma. We evaluated the prognostic impact of *IDH* mutation and high-risk genomic alterations in one of the largest multi-institutional cohorts while accounting for established prognostic factors. **Methods:** We retrospectively analyzed patients with histologically confirmed chondrosarcoma treated at the University of Miami and University of Florida. Patients with available molecular data were included. High-risk genomic alterations were defined as TP53, TERT, or cell-cycle pathway alterations. Endpoints included median overall survival (mOS), progression-free survival (mPFS) after treatment and distant metastasis-free survival (mMFS). Patients with metastatic disease at diagnosis were excluded from mMFS analyses. Multivariable Cox regression models were adjusted for age, sex, tumor grade and tumor type. **Results:** A total of 144 patients were included; 85 (59%) had NGS data. Median age was 60 years, and 46% had grade 3 disease. The majority of patients had conventional chondrosarcoma; 52 patients (36.1%) had dedifferentiated pathology. Among 64 *IDH*-mutant and 62 *IDH*-wildtype tumors, high-risk genomic alterations were identified in 48 patients, with comparable positive margin rates between *IDH*-mutant (14.1%) and *IDH*-wildtype (14.5%) cases. After multivariable adjustment for age, sex, tumor grade, and tumor type, *IDH* mutation was not independently associated with mOS (HR 1.26; $p=0.48$). However, *IDH* mutation demonstrated a trend toward inferior mPFS that did not reach statistical significance (HR 1.52; $p=0.07$) and was independently associated with inferior mMFS (HR 2.60; $p=0.004$). In contrast, high-risk genomic alterations were independently associated with inferior mOS (HR 2.45; $p=0.025$), mPFS (HR 2.94; $p=0.003$) and mMFS (HR 2.71; $p=0.009$) as compared to those patients without high-risk genomic alterations. **Conclusions:** After multivariable adjustment, *IDH* mutation conferred increased metastatic risk without an overall survival disadvantage, whereas high-risk genomic alterations consistently predicted poor outcomes across all survival endpoints. Research Sponsor: None.

Multivariable Cox regression analyses by survival endpoint in chondrosarcoma.

Endpoint	Comparison	Adjusted HR (95% CI)	p-value
Overall Survival	<i>IDH</i> mutant vs <i>IDH</i> wildtype	1.26 (0.66–2.40)	0.48
	High-risk NGS vs Low-risk NGS	2.45 (1.12–5.38)	0.025
Progression-Free Survival	<i>IDH</i> mutant vs <i>IDH</i> wildtype	1.52 (0.95–2.43)	0.077
	High-risk NGS vs Low-risk NGS	2.94 (1.45–5.96)	0.003
Metastasis-Free Survival	<i>IDH</i> mutant vs <i>IDH</i> wildtype	2.60 (1.35–5.01)	0.0043
	High-risk NGS vs Low-risk NGS	2.71 (1.28–5.74)	0.009

Survival outcomes of cabozantinib treatment with and without immune checkpoint inhibition in patients with heavily pretreated advanced sarcoma.

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Background: Cabozantinib is an oral tyrosine kinase inhibitor (TKI), with key targets including MET, VEGFR2, AXL, RET, and others. It is commonly used to treat specific carcinomas, but its efficacy in treating sarcomas is still emerging, especially in combination with immune checkpoint inhibition. The benefit of cabozantinib with or without immune checkpoint inhibition (ICI) in previously heavily treated patients with advanced sarcoma is unclear, underscoring the need for further investigation. **Methods:** We report results from a retrospective study of heavily pretreated advanced sarcoma patients who received cabozantinib with or without ICI. Eligible patients included those who had locally advanced or metastatic sarcoma and were exposed to cabozantinib for a minimum of one day. Patients who participated in the clinical trial “Randomized phase II trial of cabozantinib combined with PD-1 and CTLA-4 inhibition versus cabozantinib in metastatic soft tissue sarcoma” were excluded from this study. **Results:** There were 105 eligible patients with thirty-one different histology types, a median age of 55 years old, of which 55% were female patients. The median lines of prior treatment were four. Approximately 40.9% of patients were treated with cabozantinib alone and 59.1% were treated with cabozantinib plus either nivolumab, or nivolumab plus ipilimumab, or pembrolizumab. The progression-free survival (PFS) of the full cohort was 3.3 months. Eight patients (7.6%) obtained a partial response (PR) and forty-two patients (40.0%) had stable disease (SD) longer than 3 months, with a clinical benefit rate (CBR) of 47.6%. Partial responses occurred across a variety of histologic subtypes, including small round cell tumor, UPS, osteosarcoma, leiomyosarcoma, GIST, liposarcoma, and angiosarcoma. Stable disease was observed in a variety as well, including but not limited to LMS, synovial sarcoma, ASPS, chondrosarcoma, and osteosarcoma. The median PFS and OS for the 47.6% of patients who obtained a clinical benefit (PR + SD) were 6.9 and 22.9 months, compared to the median PFS of 2.1 months ($p < 0.001$) and median OS of 7.4 months ($p = 0.001$) for the patients with progressive disease. Several patients with aggressive histology including osteosarcoma, desmoplastic small round cell tumor, synovial sarcoma and others had PFS more than 12 months. Combination therapy with cabozantinib and an ICI accounted for the majority of PR’s observed, including the longest ongoing PR (>15.3 months) in a patient with desmoplastic small round cell tumor. **Conclusions:** In a cohort of heavily treated patients with advanced soft tissue and bone sarcoma, cabozantinib alone or with ICI showed durable CBR in nearly 50% of patients, suggesting cabozantinib alone or with ICI could be of substantial benefits to certain sarcoma patients who have very limited treatment options remaining. Research Sponsor: None.

Phase 2 study integrating early palliative care in advanced sarcoma patients for enhanced quality of life (SARQUALITY Trial: NCT06805669): An interim analysis.

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Background: Patients (pts) with advanced cancer may experience substantial symptom burden that adversely affects quality of life (QoL). Although early palliative care (EPC) integrated with standard oncologic care (SOC) has demonstrated clinical benefit, patients with sarcoma have been underrepresented in prior studies. This phase II trial evaluates whether EPC combined with SOC improves outcomes in pts with advanced sarcoma compared with SOC alone. Results from the first interim analysis are presented. **Methods:** Adult pts with advanced sarcoma who are systemic treatment naïve were randomized (1:1) to either SOC alone or with EPC. EPC intervention included palliative care (PC) review within 4 weeks of randomization, routine PC contact and access to 24-hour support. Pts receiving SOC alone are referred to PC at time of clinical need. Pts complete Edmonton Symptom Assessment System (ESAS) and EORTC QLQ-C30 questionnaires at baseline, weeks 6, 12 and 24. The primary endpoint is the change in ESAS score at week 12 compared to baseline. Secondary endpoints include EORTC QLQ-C30 score change, emergency department (ED) attendance and overall survival (OS). The aim is to accrue 136 pts, providing 80% power at one-sided 5% level of significance to detect standardised difference of 0.45 between-group in ESAS score from baseline to 12 weeks. **Results:** Enrollment commenced in July 2024. At data lock (November 2025), 44 pts were enrolled (SOC, n=21; EPC, n=23). The cohort was predominantly female (n=29, 66%), with a median age of 60 years (range 29–85). Soft tissue sarcoma accounted for 43 cases (one had osteosarcoma); 39 (89%) pts had metastatic disease and 5 (11%) had locally advanced disease. Age, gender, race, histologic subtype, and number and sites of metastases were balanced between arms. ESAS and EORTC scores for pts in EPC arm (Table 1) but ED attendances were similar (EPC-24, SOC-23). In SOC arm, symptom management interventions (radiation, surgery) occurred more frequently than the EPC arm (12 vs. 2 pts). Seven pts were referred to PC from the SOC arm (median of 3.2 months from randomization). OS data is immature. **Conclusions:** The interim results of SARQUALITY trial demonstrate EPC has an impact on ESAS and EORTC scores, however, further data required to demonstrate if there is a benefit on QoL. There was a reduction in number of symptom management interventions in EPC arm, suggesting EPC may reduce need for additional interventions. Trial accrual is ongoing. Clinical trial information: NCT06805669. Research Sponsor: None.

Mean score change at 6, 12 and 24 weeks compared with baseline.									
Week	6			12			24		
	EPC N=20	SOC N=20	p-value	EPC N=18	SOC N=18	p-value	EPC N=14	SOC N=15	p-value
ESAS (95% CI)	-1.8 (-9.0 - 5.5)	3.8 (-0.2 - 7.7)	0.172	-3.4 (-13.9 - 7.1)	3.2 (-2.8 - 9.1)	0.261	-1.8 (-11.4 - 7.9)	4.5 (0.0 - 8.9)	0.220
EORTC QLQ (95% CI)	-0.6 (-6.7 - 5.6)	4.5 (1.2 - 7.7)	0.143	0.2 (-5.6 - 6.0)	3.8 (-2.5 - 10.1)	0.379	0.0 (-6.4 - 6.4)	4.4 (-1.2 - 10.0)	0.274

Impact of concomitant medications on immune checkpoint inhibitor outcomes in sarcoma.

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Background: Immune checkpoint inhibitors (ICIs) are an established treatment for many malignancies, with an emerging role in sarcoma. While the impact of concomitant medications (CM) on ICIs has been described in other cancers, it has not been evaluated in sarcoma. We assessed the association between CM use and ICIs outcomes in sarcoma patients. **Methods:** This pooled post hoc analysis included 7 investigator-initiated phase II ICI-based trials enrolling patients with metastatic sarcoma between April 1, 2017, and May 30, 2024. Patients receiving ≥1 dose of ICIs were included. CM taken within 30 days prior to treatment initiation were defined as baseline; PRN medications were excluded. CM were recorded at each cycle through end of treatment and categorized by medication class; supplements/herbal agents included vitamins, minerals, probiotics, botanicals, amino acids, and other dietary substances. For progression-free survival (PFS), baseline and on-treatment CM were analyzed as time-dependent covariates using Cox proportional hazards models. Overall survival (OS) analyses were limited to baseline CM. Logistic regression evaluated associations between baseline CM and objective response (ORR) and immune-related adverse events (irAEs). Toxicity was graded per CTCAE v5.0. **Results:** A total of 321 patients (median age, 58 years) were included. The most common histologies were liposarcoma (all subtypes, 22%), undifferentiated pleomorphic sarcoma (22%), and leiomyosarcoma (19%); 46% had received ≥3 prior lines of therapy. ICI was combined with cytokine/oncolytic therapies (43%), targeted agents (38%), or chemotherapy (19%). After a median follow-up of 47.4 months, ORR was 18%, median PFS was 3.9 months (95% CI, 3.09–5.32), and median OS was 19.9 months (95% CI, 17.5–22.9). Grade ≥3 irAEs occurred in 25% of patients, most commonly hematologic (6%) and hepatic (5%). On-treatment use of supplements/herbal agents was associated with longer PFS (HR 0.64, 95% CI 0.50–0.82; p<0.01), while on-treatment anti-infective use was associated with shorter PFS (HR 1.55, 95% CI 1.06–2.25; p=0.02); baseline anti-infective use was not associated with PFS. Baseline supplement/herbal use was associated with longer OS (HR 0.69, 95% CI 0.53–0.90; p<0.01), whereas baseline non-opioid (HR 1.54, 95% CI 1.10–2.16; p=0.01) and opioid analgesic use (HR 2.14, 95% CI 1.45–3.14; p<0.01) were associated with shorter OS. Baseline antihistamine use showed a trend toward increased gastrointestinal irAEs (OR 2.37, 95% CI 0.97–5.98; p=0.06). No CM class was associated with ORR. **Conclusions:** Concomitant medication use is associated with differential ICI outcomes in metastatic sarcoma and warrants prospective evaluation. Research Sponsor: None.

CM	Timing	Outcome	HR
SH	OT	PFS	0.64
AI	OT	PFS	1.55
AI	BL	PFS	1.37*
SH	BL	OS	0.69
Non-OA	BL	OS	1.54
OA	BL	OS	2.14

*Not statistically significant; SH = Supplements/herbal agents, AI = Anti-infectives, OA = Opioid analgesia, OT = on-treatment, BL = Baseline.

Patient-reported global health to predict negative health outcomes in patients with advanced sarcoma.

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Background: Many patients with sarcoma deal with adverse impacts on their (QoL) related to their underlying disease as well as treatment-related effects. Unplanned hospital admissions and emergency department (ED) visits occur from uncontrolled symptoms that delay treatment and lead to poor hospital system metrics. The PROMIS Global Health v1.2 (PROMIS-10) survey is a validated tool to assess patients' physical and mental well-being at the time of the survey, with a higher number indicating a better state of health. There are limited studies evaluating longitudinal QoL assessments during sarcoma treatment. Our objective was to analyze PROMIS-10 scores for patients with advanced sarcoma and their temporal relationship with negative outcomes of interest. **Methods:** We performed a retrospective registry-based longitudinal analysis of routinely collected PROMIS-10 surveys at The Ohio State University. Patients were consented to the sarcoma registry (NCT02677961) from 6/1/2018 to 12/31/2024. We collected baseline, serial and overall change in physical and mental PROMIS-10 raw and normalized t-scores for each patient during their treatment as well as clinical characteristics, mortality, disease progression (RECIST), and ED visits/unplanned hospital admissions. Survival analyses with time-varying covariates were performed using the marginal Cox model approach for statistical analysis. **Results:** A total of 241 patients were included in the study. Patients with higher PROMIS-10 physical scores had a 13% decrease in risk of death (HR 0.87; $P < 0.001$), 3% decrease in risk of progression (HR 0.97; $P = 0.027$), and 6% decrease in risk of ED visit/unplanned hospital admission (HR 0.94; $P < 0.001$). Patients with a higher PROMIS-10 mental health score had a 7% decrease in risk of death (HR 0.93; $P < 0.001$), but no association with disease progression or risk of hospital utilization. The larger positive change in physical PROMIS-10 score from baseline to final assessment was associated with an 11% decreased risk of mortality (HR 0.89; $P < 0.001$) and 9% decreased risk of ED visit/hospital admission (HR 0.91; $P = 0.032$), but no association with progression. The larger positive change in mental PROMIS-10 score was associated with a 7% decrease in risk of progression (HR 0.93; $P = 0.010$) but there was no association with mortality or hospital utilization. **Conclusions:** We demonstrated that obtaining longitudinal patient-reported outcomes to evaluate patients' physical and mental health during sarcoma treatment can predict mortality, disease progression and ED visits/unplanned hospital admissions. Higher physical PROMIS-10 scores are strongly associated with decreased mortality and hospital utilization risk, whereas a larger positive change in mental PROMIS-10 scores is associated with decreased risk of progression. To our knowledge, this is the largest cohort (241 patients) of advanced sarcoma analyzing QoL impacts. Research Sponsor: None.

Neoadjuvant versus adjuvant chemotherapy in cardiac tumor resection: A propensity-matched analysis of perioperative and long-term outcomes.

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Background: Optimal timing of systemic therapy for primary cardiac malignancies is undefined. We compared outcomes after surgical resection when chemotherapy was administered Neoadjuvant (≤ 4 months before surgery) compared to Adjuvant (≤ 4 months after). **Methods:** We conducted a retrospective cohort study using the TriNetX database of patients undergoing cardiac tumor resection who received chemotherapy either Neoadjuvant (≤ 4 months before surgery) or Adjuvant (≤ 4 months after). Patients were matched 1:1 using propensity scores based on demographics, comorbidities, and treatment variables, yielding 220 patients per group. Primary outcomes were all-cause mortality, infection, and transfusion within 30 days of surgery. Secondary outcomes included tumor recurrence at 1 year (90–365 days), all-cause mortality, and new-onset heart failure during 1–3 years of follow-up. Time-to-event analyses were performed using Kaplan–Meier methods with log-rank testing and hazard ratios (HRs); absolute and relative risks are reported as risk differences (RD) and risk ratios (RR). **Results:** After 1:1 propensity-score matching, 220 patients were included in each group. In the perioperative period (1–30 days), all-cause mortality occurred in 18/217 patients (8.3%) in the Neoadjuvant chemotherapy group compared with 30/213 (14.1%) in the Adjuvant group (RD -0.058 , 95% CI -0.117 to 0.002 ; $p=0.057$), with a corresponding HR of 0.57 (95% CI 0.32 – 1.02 ; $p=0.056$). Infectious complications were lower with Neoadjuvant chemotherapy (12/220, 5.5%) than with Adjuvant chemotherapy (21/220, 9.5%) (RD -0.041 , 95% CI -0.090 to 0.008 ; $p=0.103$; HR 0.54 , 95% CI 0.27 – 1.10 ; $p=0.090$), while transfusion requirements were similar between groups (14.1% vs 12.3%; $p=0.57$). At 1 year (90–365 days), malignant cardiac tumor recurrence occurred in 27.7% of Neoadjuvant patients versus 21.4% of Adjuvant patients (RD $+0.064$, 95% CI -0.017 to 0.144 ; $p=0.12$; HR 1.16 , 95% CI 0.80 – 1.70). During longer-term follow-up (1–3 years), all-cause mortality was comparable between groups (44.7% vs 47.4%), with longer median survival observed in the Neoadjuvant group (791 vs 516 days; HR 0.81 , 95% CI 0.62 – 1.07 ; $p=0.14$). New-onset heart failure occurred at similar rates in both groups ($p=0.98$). **Conclusions:** In this cohort study of cardiac tumor resections, Neoadjuvant chemotherapy showed lower 30-day mortality and infection than Adjuvant chemotherapy, without significant differences in transfusion, 1-year recurrence, long-term mortality, or new-onset HF. These hypothesis generating findings suggest neoadjuvant chemotherapy is not associated with worse early or late outcomes and warrant confirmation in prospective, multi-center studies with histology-specific stratification and standardized systemic regimens. Research Sponsor: None.

Impact of regorafenib treatment on overall survival (OS) in advanced sarcoma patients.

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Background: Regorafenib has been evaluated in several sarcoma clinical trials and the common primary endpoint of these studies was Progression-Free Survival (PFS) according to RECIST, with OS as secondary endpoint. We aimed to assess the impact of regorafenib on OS using pooled analysis of REGOSARC (NCT01900743, five cohorts: liposarcoma, leiomyosarcoma, synovial sarcoma, other soft tissue sarcoma and non-adipocytic sarcoma post-pazopanib) and (NCT02389244, four cohorts: osteosarcoma, Ewing sarcoma, chondrosarcoma and chordoma). Both trials were placebo-controlled trials with potential switch to regorafenib in placebo-arm at progression. **Methods:** The primary endpoint was OS in months (mo.) from randomisation estimated by Kaplan-Meier method. The Hazard Ratio (HR) of death in a Cox model was stratified by histological . We used 2 methods for controlling regorafenib switch on OS: Rank-Preserving Structural Failure Time Model (RPSFTM; White et al. 1997) and Modified Iterative Parametric Estimation (MIPE: Zhang et al. 2016), with bootstrap-based 95%CI for both methods. Two populations were considered: in the primary analysis included all patients in both trials (n=355), and in secondary analysis excluded chordoma and liposarcoma patients (n=289), since regorafenib failed to demonstrate activity in these subtypes. **Results:** In primary analysis, the median age was 56.0 years (range, 16.0; 85.0); 325 patients (91.5%) had metastatic disease. 218 (61.4%) patients had soft tissue sarcoma and 137 (38.6%) patients had bone sarcoma. Median follow-up was 70.9 mo (IQR: 54.0-87.5). The median OS was 9.5 mo. (95%CI, 7.7-12.4) in Placebo arm versus 12.8 mo. (95%CI, 11.0-15.8) in regorafenib arm (HR: 0.85 (95%CI, 0.67-1.06); p=0.148). When correcting regorafenib switch effect, the estimated HR was 0.59 (0.31-1.25) and 0.62 (0.27-1.46) using RPSFTM and MIPE methods, respectively. **Conclusions:** In this pooled analysis, we observe a marked difference in OS, but which does not reach the , even after exclusion of chordomas and liposarcomas patients (20%-risk reduction, with p=0.083). After controlling for the switch effect, the corrected effect of regorafenib increased dramatically from 20% risk-reduction of death to a 45%-50% reduction in the population excluding chordomas and liposarcomas. Research Sponsor: None.

Prevalence of post-traumatic stress disorder and associated factors among adult sarcoma patients.

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Background: A cancer diagnosis and treatment can be extremely stressful and even traumatic for sarcoma patients. However, research on prevalence and risk factors for developing post-traumatic stress disorder (PTSD) symptoms among sarcoma patients has not been well studied.

Methods: This study used survey data from participants recruited between 4/2022 and 12/2025 for the “Cohort to Augment the Understanding of Sarcoma Survivorship Across the Lifespan” (CAUSAL) study. PTSD symptoms were assessed via the 22-item Impact of Event Scale-Revised (IES-R) at cohort enrollment, and a total IES-R score of ≥ 33 indicates PTSD symptomatology. Associations of demographics and clinical characteristics with PTSD symptoms were evaluated using logistic regression models. The association between PTSD symptoms and health-related quality of life (HRQOL), measured via T-scores for the seven core domains of the PROMIS-57 scale, was then assessed using multivariable linear regression models adjusted for potential confounders. **Results:** Among 1,112 adult sarcoma patients (509 on active treatment and 603 survivors), there are 605 females and 507 males, aged between 18 and 84 (mean age: 54.8). 18.1% of sarcoma patients/survivors reported experiencing PTSD symptoms. Female (20.5%) and younger (15.9–24.3%) sarcoma patients were significantly more likely to experience PTSD symptoms, whereas those with higher household incomes were significantly less likely to experience PTSD symptoms (11.6%–17.6%). Patients who were 5+ years post-diagnosis were less likely to experience PTSD symptoms with adjusted odds ratios (aOR) and 95% confidence intervals (CIs) of 0.56 (0.34, 0.89), compared to those who were < 18 months post-diagnosis. Regular exercise (aOR [95 CI] = 0.59 [0.42, 0.83]) and having emotional support (aOR [95 CI] = 0.63 [0.41, 0.97] for medium and 0.26 [0.15, 0.42] for high support) were inversely associated with PTSD prevalence. PTSD symptoms were significantly associated with a decreased T-score of physical function and social roles and activities with β (95% CI) of -4.2 (-5.7, -2.7) and -6.8 (-8.3, -5.2), respectively and increased scores for anxiety (β = 8.9; 95% CI: 7.6, 10.0), depression (β = 9.4; 95% CI: 8.2, 11.0), fatigue (β = 7.0; 95% CI: 5.5, 8.5), sleep disturbance (β = 7.9; 95% CI: 6.6, 9.3), and pain interference (β = 6.7; 95% CI: 5.2, 8.2). **Conclusions:** PTSD symptoms were reported by an average 18% sarcoma patients and survivors, particularly among female, younger patients, non-exercisers, and those with lower income and low emotional support. PTSD was associated with poor HRQOL. Long-term survival, regular exercise, and increased emotional support were inversely associated with the prevalence of PTSD symptoms. Psychological support and exercise programs should be offered during active cancer treatment and follow-up surveillance to reduce PTSD symptoms in sarcoma patients and survivors. Research Sponsor: None.

Enhanced local and systemic efficacy in refractory solid tumors via integrated intra-tumoral injection and radiotherapy: A study of the 'R-ISV-RO' modality.

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Background: As for most refractory solid tumors, especially sarcoma, immunotherapy still lacks meaningful improvement in their outcomes. The novel 'R-ISV-RO' in situ vaccine, in which we merged radiotherapy, intratumoral delivery of R837 and OX-40 ligand, together with systemic use of immune-checkpoint blockades, may be clinically beneficial. **Methods:** This was an exploratory, single-center, single-arm clinical trial aimed at evaluating the efficacy and safety of the 'R-ISV-RO' in situ vaccine therapy for advanced solid tumors. Thirty patients aged 18 years or older with advanced solid tumors and at least one measurable lesion were enrolled. The primary endpoint was objective response rate (ORR). Secondary endpoints included disease control rate (DCR), progression-free survival (PFS), overall survival (OS), time to progression (TTP), and clinical benefit rate (CBR). The safety of the treatment and the injection procedures were also evaluated. **Results:** The ORR and DCR for injected lesions were 44.4% and 96.3%. Sarcoma patients exhibited superior outcomes, with a 100% DCR in injected lesions. The median PFS was 15.9 months for injected lesions and median OS was 23.6 months. The abscopal effect occurred in 12 patients. 'R-ISV-RO' treatment was well tolerated, with only 6.7% of patients experiencing grade 3 or higher adverse events. Improved clinical responses were associated with enhanced CD4⁺/CD8⁺ T-cell infiltration and peripheral expansion. Metabolomics analysis revealed therapy-induced metabolic remodeling. **Conclusions:** In this exploratory trial, 'R-ISV-RO' with concurrent immunotherapy demonstrated promising efficacy for both primary and distant tumors, especially for sarcomas. Systemic immune response and metabolic remodeling were also observed after the therapy. Clinical trial information: ChiCTR2100053870. Research Sponsor: National Natural Science Foundation of China; 82272852; Foundation for studies of Clinical Trials, Drum Tower Hospital; 2022-LCYJ-MS-09; Science Fund for Distinguished Young Scholars of Jiangsu Province; BK20240017; Fundings for Clinical Trials from the Affiliated Drum Tower Hospital, Medical School of Nanjing University; 2022-LCYJ-PY-21; Nanjing Medical Science and Technology Development Foundation; YKK22086.

A phase II, multi-cohort study with pemetrexed plus cisplatin combination in patients with relapsed or refractory advanced soft tissue sarcoma: Leiomyosarcoma cohort (ALBATROSS-SARC-LMS01).

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Background: Given the promising results in previous single arm trial (NCT03809637), this histology-specific, multi-cohort, phase II trial was conducted to evaluate the efficacy and safety of pemetrexed plus cisplatin in patients with advanced and refractory soft tissue sarcoma (STS). **Methods:** In this trial (NCT04605770), we enrolled patients with metastatic and/or recurrent STS who had failed 1-2 prior cytotoxic regimens and maintained adequate performance status and organ function. The treatment regimen consisted of pemetrexed 500 mg/m² and cisplatin 75 mg/m² on day 1 of each 3-week cycle up to 6 cycles, followed by pemetrexed monotherapy. A total of 164 patients were planned for assignment into 4 histology-based cohorts (n=41 each) to account for a 10% drop-out rate: Cohort 1 (leiomyosarcoma, [LMS]), Cohort 2 (liposarcoma), Cohort 3 (vascular sarcoma), and Cohort 4 (other sarcomas). The primary endpoint was progression-free rate at 12 weeks (PFR_{12 weeks}) utilizing a Simon's two-stage design (P₁=40%, P₀=20%, $\alpha=\beta=0.1$). In the first stage, 17 patients were accrued; if at least 4 successes were observed, the cohort was to be expanded to 37 evaluable patients. To account for a 10% drop-out rate, the final enrollment target was set at 41 patients per cohort. **Results:** As of October 2025, 74 (45.1%) patients were enrolled. Among those, cohort 1 (LMS) reached full enrolment with 40 patients (median age; 53 years, female; 87.5%, 75% had received 2 prior lines of chemotherapy). Among Of 39 evaluable patients, 7 (17.9%) achieved a confirmed partial response, and 22 (53.8%) had stable disease, resulting in a disease control rate (DCR) of 74.3%. The median progression free survival was 6.3 months (95% CI, 4.9-7.6) with 74.0% of PFR_{12 weeks}. Notably, the observed DCR and PFR_{12 weeks} compare favorably with historical data for other second/third-line regimens in LMS, such as gemcitabine plus docetaxel (typical DCR 50-60%; PFR_{12 weeks} 40-50%). The median OS was 20.5 months (95% CI 14.3-26.7), with a median of 7 treatment cycles administered (range 1-31). Although treatment-related adverse events (TRAEs) occurred in the majority of patients, grade ≥ 3 TRAEs were observed in only 10 (25%) patients, mainly anemia (n=10, 25%), neutropenia (n=7, 17.5%), and nausea (n=3, 7.5%). One TREAs (drug hypersensitivity) led to treatment discontinuation due to drug hypersensitivity. **Conclusions:** The combination of pemetrexed and cisplatin was well tolerated and demonstrated promising activity in patients with relapsed, advanced STS, particularly in LMS cohort. The efficacy observed exceeded historical outcomes for standard-of-care second-line therapies, warranting further investigation in future histology-specific studies. Clinical trial information: NCT03809637. Research Sponsor: Ministry of Health & Welfare, Republic of Korea; RS-2025-02233161.

Efficacy and safety results of tazemetostat in Japanese patients with advanced epithelioid sarcoma: The phase 2 TAZETTA trial (NCCH2107).

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Background: Epithelioid sarcoma is an ultra-rare soft tissue sarcoma with limited treatment options. Tazemetostat, a selective EZH2 inhibitor, demonstrated antitumor activity in a global phase 2 study (NCT02601950) and has been approved for the treatment of epithelioid sarcoma in the US. We conducted a Japanese phase 2 study (TAZETTA; NCCH2107) as a sub-study within the framework of the nationwide rare cancer registry project in Japan (MASTER KEY Project) to evaluate the efficacy and safety of tazemetostat in patients with advanced epithelioid sarcoma. **Methods:** The TAZETTA study is a non-randomized, single-arm, phase 2 trial. Eligible patients had locally advanced or metastatic epithelioid sarcoma with loss of INI1, had received at least one prior chemotherapy including doxorubicin, had an ECOG performance status of 0–2, and at least one measurable lesion according to RECIST v1.1. Tazemetostat was administered orally at 800 mg twice daily in 28-day cycles. The primary endpoint was the progression-free survival (PFS) rate at 18 weeks by blinded independent central review. The threshold 18-week PFS rate was set at 5% and the expected rate at 30%. With a one-sided alpha of 0.05 and 80% power, the required sample size was 12 patients. To allow for ineligibility or non-treatment patients, 15 patients were planned. Secondary endpoints included PFS, overall survival (OS), objective response rate (ORR), disease control rate, duration of response, and safety. In the ancillary study, biomarker samples were collected and subjected to exploratory analysis. **Results:** Given the smooth patient accrual, 17 patients were enrolled between July 2023 and July 2024. The median age was 43 years; 13 patients were men and 4 were women. Proximal-type disease was observed in 11 patients (64.7%). The centrally assessed 18-week PFS rate was 31.3% (90% CI, 14.0–50.2), and the lower limit of the 90% CI met the predefined efficacy threshold. The median PFS was 2.9 months (95% CI, 1.6–5.6), and the median OS was 12.3 months (95% CI, 4.9–not estimable). Treatment-related adverse event with Grade ≥ 3 included lymphopenia (1pt, 5.9%). No treatment-related deaths were observed. **Conclusions:** Tazemetostat demonstrated clinically meaningful activity and a manageable safety profile in Japanese patients with advanced epithelioid sarcoma, consistent with the previous reports, supporting its role as a therapeutic option in this population. Clinical trial information: jRCT2031220523. Research Sponsor: None.

Neoadjuvant pegylated liposomal doxorubicin plus anlotinib in locally advanced soft tissue sarcoma: Clinical outcomes and multi-omics analysis from a phase II study.

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Background: Neoadjuvant therapy may improve the R0 resection and limb salvage rates in locally advanced soft tissue sarcomas (STS). This phase II trial was designed to evaluate the efficacy and safety of neoadjuvant pegylated liposomal doxorubicin (PLD) combined with anlotinib in the treatment of locally advanced STS. **Methods:** This single-center, single-arm phase II trial (NCT04765228) enrolled treatment-naïve patients with stage II/III. Patients received PLD (50 mg/m² intravenously on day 1) combined with anlotinib (12 mg orally daily on days 8–21) every 3 weeks for 2–4 cycles. Based on a one-proportion test, with $\alpha=0.05$ (two-sided) and 80% power, to detect an increase in the objective response rate (ORR) from 10% to 26%, 45 patients were planned, accounting for a 20% dropout rate. The primary endpoint was objective response rate (ORR). Secondary endpoints included progression-free survival (PFS), overall survival (OS), and safety. The exploratory endpoint was biomarker analyses. The corresponding two-sided 95% CIs were estimated using the Clopper-Pearson method. The PFS and OS were estimated using the Kaplan-Meier method. **Results:** A total of 40 eligible patients were treated between November 2020 and November 2022, of whom 34 (85.0%) underwent surgery. The median age was 46.5 years (range: 15–74 years), and 23 (57.5%) of the patients were male. Histologically, the 40 patients included 9 cases of liposarcoma (LPS), 6 cases of malignant peripheral nerve sheath tumor (MPNST), 6 cases of synovial sarcoma (SS), 3 cases of low-grade fibromyxoid sarcoma (LGFMS), 3 cases of myxofibrosarcoma (MFS), 3 cases of spindle cell sarcoma (SCS), 3 cases of undifferentiated pleomorphic sarcoma (UPS), 2 cases of leiomyosarcoma (LMS), and 5 cases of other STS. The most common sites of primary tumor were lower extremities (42.5%), waist/hip region (17.5%) and other regions. The ORR based on RECIST 1.1 was 15.0% (95% CI: 3.4%–26.6%), and the ORR of 36 patients based on Choi's criteria was 58.3%. The median PFS was 14 months (95% CI: 4.22 – 23.79 months), and the median OS was not reached. Pathological response was evaluable in 24 patients, with pathological complete response (pCR) and pathological partial response (pPR) observed in 4.2% (1/24) and 50.0% (12/24) of cases, respectively. Among 34 patients who underwent surgical resection, 30 (88.2%) achieved R0 resection, while 3 (8.8%) had R1 resection. Common treatment-related adverse events (TRAEs) of any grade included mucositis oral (52.5%), neutrophil count decreased (25.0%). Fifteen (37.5%) patients experienced at least one grade 3–4 AE. **Conclusions:** Neoadjuvant PLD combined with anlotinib exhibits promising efficacy and acceptable toxicity in patients with locally advanced STS. Results from multi-omics analyses will facilitate the screening of suitable patients in future clinical practice. Clinical trial information: NCT04765228. Research Sponsor: National Key R&D Program of China; 2023YFC2506400; National Natural Science Foundation of China; 82373385, 82272857, 82441039, 82303608; East Clinical Center of Oncology; ECCO-KY-23003.

Triplet combination of anlotinib plus nab-paclitaxel and gemcitabine (AG) as a first-line strategy for advanced primary cardiac angiosarcoma: A high-volume center experience.

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Background: Primary cardiac angiosarcoma (PCAS) is an exceedingly rare and lethal mesenchymal malignancy characterized by aggressive growth and high metastatic potential. Despite the use of taxane-based regimens, the prognosis remains dismal, with a historical median overall survival (mOS) of approximately 11 months. Given the highly vascular nature of PCAS, we hypothesized that integrating a multi-target anti-angiogenic TKI (anlotinib) with cytotoxic chemotherapy could synergistically improve outcomes. This study evaluated the efficacy and safety of anlotinib plus nab-paclitaxel and gemcitabine (AG) in advanced PCAS. **Methods:** We retrospectively analyzed patients with metastatic or unresectable PCAS treated at Zhongshan Hospital, Fudan University. The triplet regimen consisted of anlotinib (8-12 mg QD, days 1-14, q3w), nab-paclitaxel (200 mg), and gemcitabine (1000 mg/m²) on days 1 and 8 every 3 weeks. The primary endpoint was progression-free survival (PFS). Secondary endpoints included objective response rate (ORR), overall survival (OS), and safety (CTCAE v5.0). Survival outcomes were estimated using the Kaplan-Meier method and compared via log-rank tests. **Results:** A total of 24 patients were included, with a median age of 44 years. Most tumors (91.7%) originated in the right atrium, and 70.8% of patients received this regimen as first-line therapy. **Efficacy:** At a median follow-up of 31.4 months, the ORR was 62.5% and the DCR was 95.8%. **Survival:** The median PFS was 9.5 months (95% CI, 8.4-20.7). Notably, the median OS reached 24.9 months (95% CI, 15.2-NR), significantly exceeding historical benchmarks. **Prognostic Indicators:** Subgroup analysis identified liver metastasis (45.8%) as a significant negative prognostic factor for PFS ($p = 0.018$). Additionally, a numerical trend toward shorter survival was observed in patients with baseline D-dimer > 5 mg/dL (Median OS: 5.5 vs. 10.5 months; $p = 0.428$). **Safety:** Treatment-related adverse events (TRAEs) of any grade occurred in 95.8% of patients. Grade ≥ 3 TRAEs (41.7%) were primarily hematological (neutropenia, thrombocytopenia) and were manageable via dose modification. No severe treatment-related cardiotoxicity was observed. **Conclusions:** The triplet combination of anlotinib and AG demonstrates unprecedented survival benefits and a manageable safety profile in advanced PCAS. With a mOS exceeding twice the historical data, this regimen represents a potent new treatment strategy. Liver involvement serves as a critical prognostic indicator for risk stratification, while the clinical significance of baseline D-dimer levels as a surrogate marker for tumor burden warrants further investigation in larger cohorts. Research Sponsor: None.

Outpatient rehabilitation for adults with soft tissue sarcoma: Examining real-world service utilization and outcomes.

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Background: Soft tissue sarcoma (STS) and its treatments frequently result in substantial physical morbidity, leading to impaired function and reduced quality of life. Rehabilitation can improve outcomes, yet real-world utilization and effectiveness in this population remain poorly understood. This study describes outpatient rehabilitation service use among adults with STS and examines changes in physical function and quality-of-life outcomes. **Methods:** Electronic medical record data from outpatient rehabilitation encounters were retrospectively analyzed for adults with a STS diagnosis (identified by ICD code) who completed ≥ 2 visits and had pre- and post-treatment outcome measures available. Rehabilitation characteristics were examined descriptively, including visits, care duration, service type, and treatment indications (identified by ICD code). PROMIS-Physical function (PF) was the primary outcome. Secondary outcomes were PROMIS-Global physical health (GPH), -Ability to participate in social roles and activities (SRA), and -Global mental health (GMH). Mixed-effect models assessed change in T-scores, adjusting for covariates (age, visits per week, care duration) and accounting for within-subject correlation. Estimated marginal (EM) means are reported. Change scores were compared to the established minimal important change (MIC, 2 points) to determine clinical relevance. **Results:** A total of 151 patients met inclusion criteria (mean age 56.0 ± 16.7 years; 57% female). Most received physical therapy (86.1%), with fewer receiving occupational therapy (13.2%). The median episode of care was 8.3 weeks (IQR 4.3–16.0), with a mean of 1.6 ± 0.7 visits per week. Common treatment indications included pain (37.9%), weakness/deconditioning (35.8%), gait/balance (27.5%), followed by lymphedema (8.5%), fatigue (5.9%), wound/post-surgery care (5.5%), and neuropathy (3.1%). Significant improvements were observed in PF (+2.48, SE: 0.57), GPH (+2.64, SE: 0.50), and SRA (+2.64, SE: 0.57) ($p < .001$), each surpassing the MIC. No significant change was observed in GMH (-0.39, SE: 0.48, $p = .419$). **Conclusions:** In this real-world cohort of adults with STS, outpatient rehabilitation averaged 8 weeks of care and 1–2 visits per week, most commonly addressing pain, weakness, and gait/balance deficits. Significant and clinically meaningful improvements were observed in physical function and the physical and social aspects of quality of life; mental health was not significantly affected. These findings support the role of rehabilitation as an important component of multidisciplinary sarcoma care and underscore the need for complementary strategies to address psychosocial outcomes. Research Sponsor: None.

PROMIS T-scores, EM mean (SE).		
Outcome	Pre	Post
PF	36.26 (0.50)	38.74 (0.57)
GPH	39.44 (0.52)	42.08 (0.56)
SRA	43.17 (0.56)	45.82 (0.65)
GMH	47.40 (0.60)	47.02 (0.63)

The investigator-initiated trial (IIT) of GO306 injection, a recombinant oncolytic vaccinia virus, in patients with advanced soft tissue sarcomas.

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Background: Oncolytic vaccinia viruses exert anti-tumor effects via direct lysis and systemic immunity induction. Advanced soft tissue sarcomas (STS) are heterogeneous malignancies with limited post-standard therapy options. GO306 is a oncolytic virus expressing PD-1/TGFβ inhibitors for tumor-selective replication and enhanced immunity. We report GO306's preliminary safety and tolerance in pretreated advanced STS. **Methods:** This open-label, single-arm IIT enrolled histologically confirmed advanced STS refractory to standard therapy. A 3+3 dose-escalation design was used, with intratumoral GO306 at 3×10^7 PFU, 3×10^8 PFU and 1×10^9 PFU. A 21-day DLT assessment period was set. Tumor assessment was done on day 28 per RECIST v1.1. Primary endpoints: MTD, DLTs, safety; secondary endpoints: OS, ORR, PFS, immunogenicity, viral shedding. **Results:** As of Dec 5th, 2025, 10 participants were enrolled across 3 dose cohorts, 9 completed the 21-day DLT assessment (1 non-DLT withdrawal). Demographics: median age 52.4 years, 80% male, ECOG 1-2. No DLTs were observed; MTD not reached. A total of 110 AEs were reported, including 52 treatment-related adverse events (TRAEs), 98.8% (51/52) were grade 1-2, with 1 grade 3 pulmonary infection (SAE due to prolonged hospitalization). No grade 4-5 TRAEs occurred. Most common AEs: pyrexia (60%, grade 1-2), followed by hypokalemia, hypocalcemia and hypoalbuminemia (40% each, grade 1-2). Efficacy was evaluable in 8 participants: 87.5% (7/8) SD and 12.5% (1/8) PD. Survival data: 2 participants with OS > 5 months, 1 alive at 260 days (all received subsequent anti-tumor therapies), 2 with 90-day survival documented. Viral shedding: GO306 was below the limit of quantification (BLQ) in feces, urine, throat swabs, and plasma on day 3/7, undetectable on day 30 (some samples pending). PD-1 inhibitor was detectable in 6/10 participants (29.91~19073.64 ng/mL); TGFβ inhibitor in 7/10 participants (80.39 to 460.31 ng/ml). **Conclusions:** Intratumoral GO306 showed favorable safety profile and manageable TRAEs in pretreated advanced STS. Preliminary efficacy support phase I/II expansion and combination studies with other immunotherapies or targeted therapies. Clinical Trial Registration Number: ChiCTR2400088508. Xianhai Zhu and Hu Liu contributed equally as corresponding author. Clinical trial information: ChiCTR2400088508. Research Sponsor: None.

Demographic and overall response of participants.

Screen No.	Age	Gender	ECOG	Malignancy Diagnosis	Overall Response*
S002	60	M	1	Retroperitoneal Liposarcoma	SD
S003	59	F	2	Liposarcoma	SD
S006	70	M	1	Leiomyosarcoma	SD
S007	60	M	2	Retroperitoneal Liposarcoma	PD
S010	48	M	1	Retroperitoneal Leiomyosarcoma	SD
S011	48	M	1	Retroperitoneal Leiomyosarcoma	SD
S012	56	M	1	Chondrosarcoma	SD
S013	30	M	1	Synovial Sarcoma	SD

Abbreviations: *Per RECIST V1.1; 8/10 enrolled participants had evaluable day-28 tumor assessments and are included.

Cardiac safety of aldoxorubicin compared to doxorubicin: Integrated results from two randomized studies in advanced soft tissue sarcoma.

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Background: Doxorubicin clinical benefit is limited by cumulative, irreversible cardiotoxicity that restricts dosing. Aldoxorubicin is an albumin-binding prodrug of doxorubicin designed to enhance tumor delivery while reducing systemic exposure to cardiotoxic metabolites such as doxorubicinol. Prior reports suggest improved cardiac tolerability of aldoxorubicin, but no integrated analysis across randomized studies has been presented. **Methods:** Cardiac safety data were analyzed from two randomized studies, INNO-206-STS-P2-01 (NCT01514188) and ALDOXORUBICIN-P3-STS-01 (NCT02049905), comparing aldoxorubicin with doxorubicin in advanced soft tissue sarcoma. Left ventricular ejection fraction (LVEF) was assessed at baseline and prespecified intervals during and after treatment. Outcomes included mean and change-from-baseline LVEF, proportion of patients with LVEF <45%, treatment-emergent heart-failure and cardiovascular adverse events (AEs), and composite endpoints integrating LVEF decline and cardiac AEs. Cumulative doxorubicin-equivalent dose was calculated using a 0.74 conversion factor. **Results:** Across both studies (N≈383), baseline demographics and cardiac risk factors were balanced. Aldoxorubicin was administered at approximately 3.5-fold higher doxorubicin-equivalent cumulative doses than doxorubicin. Despite higher exposure, aldoxorubicin was associated with smaller mean LVEF declines (pooled lowest on-treatment change -3.17% vs -5.77%; nominal $p < 0.05$). Approximately three-fold more doxorubicin-treated patients reached LVEF <45% (1.1% vs 3.8%). Composite endpoints favored aldoxorubicin, including HF-AE plus LVEF <45% (0.7% vs 3.4%), HF-AE plus ≥10-point decline (2.0% vs 4.6%), prespecified cardiovascular AE plus LVEF <45% (0.3% vs 1.1%), and prespecified cardiovascular AE plus ≥10-point decline (1.4% vs 4.6%). Treatment-emergent prespecified heart-failure events occurred less frequently with aldoxorubicin (3.0% vs 6.9%). LVEF-exposure plots showed higher LVEF with aldoxorubicin despite substantially higher cumulative exposure. In Phase 1 aldoxorubicin pharmacokinetic data, the doxorubicinol-to-doxorubicin exposure ratio was ~5–6%, compared with ~40–60% reported for conventional doxorubicin, consistent with lower systemic doxorubicinol burden and supporting the observed cardiac safety findings. **Conclusions:** Across two randomized studies, aldoxorubicin demonstrated a consistently more favorable cardiac safety profile than doxorubicin despite higher cumulative exposure, with smaller LVEF declines and fewer heart-failure-related events. These findings support aldoxorubicin as a potentially safer anthracycline option for patients requiring sustained exposure. Research Sponsor: Gemini Therapeutics, Inc.

Neo-adjuvant radiation and intratumoral immunotherapy followed by surgery: The NARIS trial for extremity soft tissue sarcoma.

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Background: Patients with STS who failed to respond to standard treatment have limited subsequent treatment options. Radiotherapy combined with immunotherapy has demonstrated efficacy in certain STS subtypes, such as undifferentiated pleomorphic sarcoma (UPS); however, perioperative strategies still require optimization to further improve local control and reduce adverse events, particularly for patients with multiple recurrences yet seeking limb preservation. **Methods:** Patients with pathologically confirmed extremity STS without metastases were enrolled. Eligible participants received two neoadjuvant cycles administered every three weeks. Each cycle consisted of hypofractionated radiotherapy (a total of $5 \text{ Gy} \times 4$ fractions across two cycles) combined with intratumoral injection of a PD-L1 (TQB2450) monoclonal antibody. **Results:** A total of 15 patients were screened, of whom 11 met the eligibility criteria and provided written informed consent. Except for one patient with disease progression after standard chemoradiotherapy, other patients had recurrent disease following one to three prior curative resections at baseline. The ORR and DCR were 36.4% (95% CI, 10.9–69.2%) and 90.9% (95% CI, 58.7–99.8%), respectively. One patient has not yet undergone surgery. Among the 10 patients who received surgery, one achieved a pCR, and two achieved MPR. All three cases occurred in UPS patients. In the 10 evaluable patients with STS, the median percentage of tumor necrosis and fibrosis was 63.5% (IQR 17.5–88.75%), and the median residual viable tumor percentage was 36.5% (IQR 11.25–82.5%). Subgroup analysis showed that the median percentage of tumor necrosis and fibrosis in UPS patients was 97% (IQR 88–99.25%), compared with 25% (IQR 10–55%) in other histological subtypes. The pCR rate and MPR rate in UPS patients were 25% (1/4) and 75% (3/4), respectively. During the neoadjuvant phase, the main TEAEs were local swelling and decreased lymphocyte counts, which were reversible during treatment intervals. No grade 3 TEAEs or immune-related adverse events were observed. Postoperative complications in the 10 surgical patients were as expected and mainly included local soft tissue edema, pain, local stiffness, and limb numbness. No delayed wound healing or surgical site infections were observed. **Conclusions:** Compared with current clinical studies in STS that employ conventionally fractionated radical radiotherapy and intravenous immune checkpoint inhibitors, this study utilized a lower total radiation dose delivered in larger fractions combined with intratumoral administration of immunotherapy, achieving comparable disease control with manageable toxicity. It may be clinically valuable for patients with recurrent disease after multiple surgeries or those with prior exposure to local radiotherapy. Clinical trial information: ChiCTR2200060659. Research Sponsor: National Natural Science Foundation of China; 82272852; Science Fund for Distinguished Young Scholars of Jiangsu Province; BK20240017; Foundation for studies of Clinical Trials, Drum Tower Hospital; 2023-LCYJ-MS-24.

Effect of pimicotinib on tumor response and physical function (PF) by tumor location in patients with tenosynovial giant cell tumor (TGCT): Results from the phase 3 MANEUVER trial.

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Background: TGCT is a rare, locally-aggressive, soft-tissue tumor driven by colony-stimulating factor-1 (CSF-1) overproduction, often leading to impaired PF. Pimicotinib (pimi), an oral, highly-selective CSF-1 receptor inhibitor, demonstrated robust tumor responses, clinically meaningful symptomatic and functional improvements, and a tolerable safety profile in patients (pts) with TGCT in the global Phase 3 MANEUVER trial (NCT05804045). Here, we report the effects of pimi on tumor response and PF in joints most commonly affected by TGCT.

Methods: In MANEUVER, symptomatic adult pts with unresectable TGCT were randomized 2:1 to once-daily pimi 50 mg or placebo for 24 weeks (Part 1). After Part 1, eligible pts received open-label pimi for 24 weeks (Part 2), followed by an ongoing long-term extension period (Part 3). Longer-term objective response rate (ORR) by blinded independent review committee (BIRC) per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, Range of Motion (ROM) responses, and Patient-Reported Outcomes Measurement Information System-PF (PROMIS-PF) scores from Part 1 to Part 3, up to data cut-off, are reported by tumor location for pts randomized to pimi in Part 1. **Results:** At baseline, 63 pts were randomized to pimi; 71.4% were female and median age was 41.0 years (range 18–69). Median follow-up was 14.3 months and median treatment duration was 14.2 months. Most pts had diffuse TGCT (84.1%), with an affected lower extremity (85.7%), particularly the knee (52.4%). Tumor responses to pimi were comparable for localized (n=8) and diffuse (n=53) TGCT based on ORR by BIRC per RECIST v1.1 (95% CI): 87.5% (47.3, 99.7) vs 75.5% (61.7, 86.2), respectively. ORRs (95% CI) were comparable for pts with lower extremity (n=54) tumors and upper extremity (n=9) tumors: 75.9% (62.4, 86.5) vs 77.8% (40.0, 97.2), respectively, and for knee tumors (n=33) vs other (n=30) locations: 75.8% (57.7, 88.9) vs 76.7% (57.7, 90.1), respectively. Knee ROM improved from baseline to Week 49 (mean change: 8.9 [SD 8.4]). PROMIS-PF scores for lower extremity measures such as walking, climbing stairs, standing, and bending/kneeling improved from baseline (n=54) to Week 49 (n=43) (Table). **Conclusions:** Pimi provided sustained, clinically meaningful benefits in pts with TGCT, including durable tumor shrinkage and improved ROM and PF, regardless of tumor location. These results support pimi as an effective treatment option for patients with unresectable TGCT. Clinical trial information: NCT05804045. Research Sponsor: Abbisko Therapeutics; Merck KGaA, Darmstadt, Germany.

Longer-term PROMIS-PF scores per item from baseline to week 49.

PROMIS-PF score ^a Mean (SD)	Baseline (N=54)	Week 49 (N=43)
Walk for ≥15 minutes	3.9 (1.0)	4.6 (0.6)
Climb stairs	3.3 (1.1)	4.2 (0.8)
Stand for 1 hour	2.9 (1.2)	3.7 (1.3)
Bend, kneel, or stoop	2.7 (1.3)	3.6 (1.2)

^a1-Unable to do; 2-With much difficulty; 3-With some difficulty; 4-With a little difficulty; 5-Without any difficulty.

Longer-term safety of pimicotinib in tenosynovial giant cell tumor (TGCT): Integrated analysis of phase 1 and phase 3 MANEUVER trial data.

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Background: TGCT is a rare, locally-aggressive neoplasm associated with significant morbidity and functional impairment. Colony-stimulating factor-1 receptor (CSF-1R) inhibitors are effective for unresectable TGCT, but current options may be limited by their long-term safety and tolerability. In the Phase 3 MANEUVER trial, pimicotinib (pimi), a highly-selective CSF-1R inhibitor, demonstrated robust tumor responses, clinically meaningful symptomatic and functional improvements, and a tolerable safety profile. This integrated analysis evaluated the longer-term safety of pimi from Phase 1 and 3 trials. **Methods:** Data for adult patients (pts) with TGCT treated with pimi 50 mg once daily from Phase 1 (NCT04192344, cut-off Dec 31, 2024) and Phase 3 (NCT05804045; MANEUVER, cut-off Mar 12, 2025) trials were pooled for an integrated safety analysis. The open-label Phase 1 study assessed safety, tolerability, and pharmacokinetics of pimi in advanced solid tumors. MANEUVER evaluated efficacy and safety of pimi in unresectable TGCT across a 24-week, double-blind, placebo-controlled phase; a 24-week open-label pimi treatment phase; and an ongoing long-term extension. All treatment-emergent adverse events (TEAEs) and adverse events of clinical interest (AECI) were analyzed and reported as frequencies. **Results:** In total, 158 pts were included; 65.8% were female and median age was 40.0 (range 18–76) years. Median pimi exposure was 385.5 days; 12.7% of pts had prior exposure to systemic therapy. TEAEs of any grade were reported by 99.4% of pts (Table); most pts reported a maximum grade of 1 (8.9%; n=14/158) or 2 (53.2%; n=84/158). The most reported AECI of any grade by pts were blood creatine phosphokinase (CPK) elevation (72.2%), aminotransferase elevation (59.5%), edema (excluding periorbital edema [POE]) (54.4%), rash (46.2%) and pruritus (43.0%); 20.9% reported fatigue. There was no evidence of cholestatic hepatotoxicity or drug-induced liver injury. The most common AECI leading to dose reduction were rash (5.1%) and edema (excluding POE) (3.2%); for dose interruption, blood CPK elevation (13.9%) and rash (13.3%) were most common. Most AECI resolved/improved following dose reduction or interruption. Treatment discontinuation due to AECI was rare (face edema, 0.6%; rash, 0.6%). Concomitant medication was most commonly used for rash (n=38/73), pruritus (n=31/68), and edema (n=22/86). **Conclusions:** Pimi showed sustained tolerability with no new safety signals, confirming a favorable safety profile in Phase 1 and 3 trials during extended treatment of >1 year in a larger TGCT population. Clinical trial information: NCT04192344; NCT05804045. Research Sponsor: Abbisko Therapeutics; The healthcare business of Merck KGaA, Darmstadt, Germany.

Summary of TEAEs.

TEAE	Pts (N=158) n (%)
Any	157 (99.4)
Grade ≥3	59 (37.3)
Serious	17 (10.8)
DR serious	1 (0.6)
Leading to dose reduction	33 (20.9)
Leading to dose interruption	95 (60.1)
Leading to discontinuation	8 (5.1)
Resulting in death	1 (0.6)
DR resulting in death	0

DR, drug related.

Efficacy and safety of engineered TCR-T cell therapy (afami-cel, lete-cel) in pediatric synovial sarcoma.

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Background: Synovial sarcoma (SyS) represents ~ 5% of adult soft tissue sarcomas, however, SyS is the most common non-rhabdomyosarcoma soft tissue sarcoma in the pediatric population. Both lete-cel, an engineered TCR-T cell therapy targeting NY-ESO-1, and afami-cel, an engineered TCR-T cell therapy targeting MAGE-A4, have shown efficacy and an acceptable safety profile in adult patients with SyS. We report here the largest cohort of pediatric SyS patients treated with either afami-cel or lete-cel. **Methods:** Pediatric SyS patients (pts) were treated on four phase II trials: lete-cel SyS Pilot study (NCT01343043), lete-cel IGNYTE-ESO trial (NCT03967223), afami-cel SPEARHEAD-1 (NCT04044768) and SPEARHEAD-3 (NCT05642455). Initial data from SPEARHEAD-3 will be available and added at the time of presentation. Eligibility for this analysis: advanced (unresectable/metastatic) SyS, human leukocyte antigen (HLA)-A*02, NY-ESO-1 or MAGE-A4 expression, baseline ECOG 0-1 and received any dose of lete-cel or afami-cel as a single infusion. Key efficacy endpoints: independent review-assessed overall response rate (ORR) per RECIST v1.1, best overall response, duration of response (DoR). Key safety endpoints: adverse events (AEs), serious AEs, AEs of special interest (ex. Cytokine release syndrome (CRS)). Data is presented separately for lete-cel and afami-cel. **Results:** Seven pediatric pts (age 10 to 17) were treated with lete-cel for advanced disease. The median lete-cel dose was 4.9×10^9 transduced cells. The ORR was 43% (3/7 pts, 2 PR, 1 CR). The duration of response was 2.83, 7.39, and 7.39 months respectively; one response was ongoing at the time of this analysis. Pediatric pharmacokinetics and exposure-response data were in agreement with data from adult pts. Seven pediatric pts (age 13 to 16) were treated with afami-cel for advanced disease. The median afami-cel dose was 8.2×10^9 transduced cells. The ORR was 28.6% (2/7 pts, 2 PR). The duration of response was 4.7 and 17.4 months respectively; one response was ongoing at the time of this analysis. Similar pharmacokinetics were observed in pediatric pts compared to adult pts. CRS was common occurring in >50% of pts for both lete-cel and afami-cel; events were grade 1 or 2, except one patient with lete-cel experiencing grade 3 CRS. Cytopenias after lymphodepletion and T cell infusion were the most common grade 3 or 4 adverse events (>30% of pts) for both therapies. **Conclusions:** Engineered TCR-T cell therapy targeting NY-ESO-1 (lete-cel) or MAGE-A4 (afami-cel) has shown responses and durable responses in the pediatric SyS population. The safety profile in this age group is consistent with that observed in the adult population. TCR-T represents a potential new treatment paradigm for pediatric SyS patients. Further studies should help to determine the optimal timing for this cellular therapy. Additional Information: Coauthor Brian Van Tine, MD, died Nov 2025. Clinical trial information: NCT01343043, NCT03967223, NCT04044768, NCT05642455. Research Sponsor: Adaptimmune LLC; USWM CT, LLC.

Outcomes of malignant peripheral nerve sheath tumors in neurofibromatosis type 1 and sporadic patients: A 25-year experience from a sarcoma referral center.

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Background: Malignant peripheral nerve sheath tumors (MPNST) are rare, aggressive soft-tissue sarcomas frequently associated with neurofibromatosis type 1 (NF1). Prospective trials are scarce, and prognostic factors and treatment effects remain incompletely defined. **Methods:** We conducted a retrospective observational cohort study of 200 patients (215 tumor episodes) with histologically confirmed MPNST treated at a national sarcoma referral center between 2000 and 2025. Overall survival (OS) and progression-free survival (PFS) were estimated via Kaplan–Meier methods. Multivariable Cox models with multiple imputation (MICE, m=40) were adjusted for clinical factors. Restricted mean survival time (RMST) at 5 years quantified absolute survival differences. Interaction analyses assessed heterogeneity of radiotherapy (RT) effects. **Results:** Median age was 40 years; 51.5% of patients had NF1. Median OS and PFS were 74.6 and 9.1 months, respectively. NF1-associated MPNST had significantly shorter OS (28.5 vs 141.0m; p=0.012), with a 5-year RMST reduction of 8.5 months (95% CI -15.0 to -2.3; p=0.01). In the multivariable Cox model with multiple imputation, advanced stage (HR 2.28; 95% CI 1.68–3.09; p<0.001), higher FNCLCC grade (HR 1.95; 95% CI 1.39–2.75; p<0.001), NF1 status (HR 1.67; 95% CI 1.11–2.51; p=0.014), central tumor location (HR 1.63; 95% CI 1.02–2.60; p=0.041), and increasing age (HR 1.04 per year; 95% CI 1.02–1.05; p<0.001) were independently associated with inferior OS, whereas female sex was strongly protective (HR 0.43; 95% CI 0.29–0.66; p<0.001). Major biopsy-surgery histologic discordance occurred in 21.6% of cases, and diagnostic delays > 60 days in 28.4%. A significant interaction was observed between RT and surgical margins (p_{int}=0.028): RT markedly improved OS in R1/R2 resections (HR 0.31, 95% CI 0.16–0.61) and in locally advanced disease, but not after R0 resection. In NF1 patients, imaging-detected tumors had better surgical margins and lower risk of synchronous metastasis despite similar tumor size. **Conclusions:** MPNST outcomes remain poor, particularly in NF1. Radiotherapy confers a clear survival benefit in high-risk surgical contexts. Optimizing diagnostic pathways, especially in NF1 patients, may improve outcomes. Research Sponsor: None.

Survival Predictors (Multivariable OS)	Hazard Ratio (95% CI)	p-value
Stage	2.28 (1.68–3.09)	<0.001
FNCLCC Grade	1.95 (1.39–2.75)	<0.001
NF1-associated	1.67 (1.11–2.51)	0.014
Central Location	1.63 (1.02–2.60)	0.041
Female Sex	0.43 (0.29–0.66)	<0.001
RT Benefit in R1/R2 Resection	0.31 (0.16–0.61)	0.001

Adverse events and their management in patients with tenosynovial giant cell tumor (TGCT) treated with pimicotinib, after longer-term follow-up from the global phase 3 MANEUVER trial.

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Background: TGCT is a rare, locally aggressive, soft-tissue tumor associated with significant morbidity. Pimicotinib (pimi) is an oral, highly selective, small molecule colony-stimulating factor-1 receptor (CSF-1R) inhibitor. In the Phase 3 MANEUVER trial (NCT05804045), the primary and key secondary endpoints were met; pimi demonstrated robust tumor responses and symptomatic and functional improvements, with a tolerable safety profile. Here, we report the longer-term safety profile and adverse event management strategies with at least one year of pimi treatment. **Methods:** Adults patients (pts) with symptomatic unresectable TGCT were randomized (2:1) to pimi 50 mg once daily or placebo for 24 weeks (Part 1), followed by open-label pimi for an additional 24 weeks (Part 2) and an extension phase. Treatment-emergent adverse events (TEAEs) were monitored for 30 days after the last dose and graded using the Common Terminology Criteria for Adverse Events, version 5.0. **Results:** In total, 63 pts received pimi (median follow-up: 14.3 months). The most frequent laboratory abnormality TEAE was increased creatinine phosphokinase (CPK; 71.4%) and the most common clinical TEAE was pruritus (60.3%). Fatigue occurred in 28.6% of pts. Most TEAEs were Grade 1–2 (Table). Grade ≥ 3 TEAEs occurred in 46.0% of pts, primarily elevated CPK (15.9%) and rash (6.3%), with no Grade ≥ 3 periorbital or facial edema observed. TEAEs were managed with dose interruptions (66.7%; median 11 days) and reductions (25.4%), maintaining a high median percentage intended dose (88.2%). Discontinuations were infrequent (6.3%). Concomitant medications were commonly used for AE management; local corticosteroids and antihistamines for rash and pruritus, and diuretics for edema. **Conclusions:** This analysis confirmed the distinct and manageable safety profile of pimi. Most TEAEs were low grade and managed through dose modifications and standard concomitant medications, enabling sustained dosing and minimal discontinuations. These findings support the longer-term tolerability of pimi in TGCT. Clinical trial information: NCT05804045. Research Sponsor: Abbisko Therapeutics; Merck KGaA, Darmstadt, Germany.

Grades of most common TEAEs ($\geq 30\%$) in patients treated with pimi in the MANEUVER phase 3 trial.

TEAEs, n (%) ^a	Any grade	Grade 1	Grade 2	Grade ≥ 3
Blood CPK increased ^b	45 (71.4)	20 (31.7)	15 (23.8)	10 (15.9) ^c
Blood LDH increased ^b	36 (57.1)	35 (55.6)	1 (1.6)	0
AST increased ^b	35 (55.6)	33 (52.4)	2 (3.2)	0
Amylase increased ^b	24 (38.1)	16 (25.4)	8 (12.7)	0
Pruritus ^d	38 (60.3)	26 (41.3)	10 (15.9)	2 (3.2)
Face edema ^d	31 (49.2)	22 (34.9)	9 (14.3)	0
Rash ^d	24 (38.1)	18 (28.6)	2 (3.2)	4 (6.3)
Periorbital edema ^d	23 (36.5)	18 (28.6)	5 (7.9)	0

^aTEAEs were not mutually exclusive; patients may have had more than one TEAE.

^bAsymptomatic laboratory abnormalities.

^cIncluded one patient with Grade 4 event.

^dClinical adverse events.

LDH, lactate dehydrogenase; AST, aspartate aminotransferase.

Phase I trial of LB-100 plus doxorubicin as first-line of advanced soft tissue sarcomas: A Spanish Sarcoma Group (GEIS) study.

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Background: In sarcomas, blocking the phosphatase PP2A with LB-100 enhanced doxorubicin effectiveness, reducing tumor growth and metastases in *in vivo* experiments. Mechanistically, LB-100 inhibited ATM/ATR-activated DNA damage response. The combination of doxorubicin and LB-100 significantly shrank tumor xenographs compared with either compound alone. The recommended phase 2 dose (RP2D) for LB-100 in monotherapy was 2.33 mg/m²/d x3 days in a phase I in progressive solid tumors, reporting 1 partial response and 16 SD (including the 2 enrolled patients with sarcoma) out of 20 patients. Based on prior data, we designed a phase I trial (NCT05809830) combining doxorubicin (D) and LB-100 (L) for first-line advanced sarcomas. **Methods:** Adult patients with advanced soft tissue sarcomas and no prior anthracycline treatment were enrolled. The main endpoint was to determine the RP2D. Secondary endpoints were to evaluate the safety profile, efficacy (PFS, ORR, OS), QoL, and translational research. Dose levels were defined as follows, I: D 60 L 1.75; II: D 75 L 1.75; III: D 75 L 2.33; A -I dose-level was defined as D 60, L 1.25. L was administered on days 1 to 3 in a 2-hour IV infusion, followed by D in a 20-minute IV infusion on day 1 of each cycle. After 6 cycles of combination, L was administered as a maintenance phase until disease progression or unacceptable toxicity. **Results:** Between June 2023 and September 2024, 14 out of 17 screened patients were recruited, with 12 eligible for DLT evaluation. The non-DLT-evaluable patients were explained by the use of G-CSF and the altered sequence of drug administration during the first cycle. No DLTs were reported. Grade 3-4 treatment-related adverse events were neutropenia 42.9%, febrile neutropenia 21.4%, LVEF reduction 14.3%, and one patient each for nausea, anemia, and lymphopenia (7.1%). There were 2 partial responses (14%), 6 stabilizations (43%), and 6 progressions (43%) following RECIST criteria of 14 evaluable patients. Responses were seen in patients with UPS and myxofibrosarcoma. The mPFS was 5.7 months (95% CI 0-13.3), and the mOS was 16.7 months (95% CI NA). The only QoL items of EORTC-QLQ-C30 that significantly changed (impaired) between baseline and before the 3rd cycle were nausea and diarrhea. There were 1SD and 2 PD of 3 patients in the first dose-level, 1 PR and 3SD of 4 patients in the second dose-level, and 1 PR, 2 SD, and 4 PD of 7 patients in the third dose-level. In our preclinical investigations, the highest concentrations of L induced an antagonistic effect with D. **Conclusions:** The RP2D is L1.75 and D 75 based on tolerance and activity, and it deserves to be tested in phase II trials. Clinical trial information: NCT05809830. Research Sponsor: None.

Who really benefits from chemotherapy in high-risk localized soft tissue sarcoma? A virtual twin analysis of ISG-STs 1001.

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Background: Randomized trials of perioperative chemotherapy in high-risk localized extremity/truncal soft tissue sarcoma (etSTS) show modest average survival benefits, leaving uncertainty about which patients derive clinically meaningful benefit. Conventional hazard ratio-based reporting reflects population-level effects but offers limited guidance for individual decisions. Counterfactual approaches, such as the virtual twin framework, enable estimation of patient-specific outcomes under alternative treatment strategies, translating randomized evidence into clinically interpretable absolute benefit measures. **Methods:** Individual patient data from the ISG-STs 1001 randomized trial in high-risk localized etSTS with updated follow-up were analyzed using a virtual-twin framework with counterfactual predictions to estimate each patient's outcomes under alternative treatment scenarios: standard epirubicin-ifosfamide (EI) vs histotype-tailored (HT) chemotherapy (proxy for no effective chemotherapy). Patients with myxoid liposarcoma were excluded. Cox proportional hazards models for overall survival (OS) and disease-free survival (DFS) were adjusted for pretreatment covariates. For each patient, counterfactual 5-year OS and DFS probabilities under EI and HT were estimated and individualized absolute treatment effects were defined as the difference between counterfactual predictions. Bootstrap resampling was used to quantify uncertainty and treatment benefit explored across levels of baseline risk and tumor characteristics. **Results:** The cohort included 218 pts (median follow-up 116 months). In covariate-adjusted models, mean absolute improvement in 5-year OS with EI was 7.5% (95%CI: 4.5%-10.2%). Absolute OS benefit was inversely correlated with Sarcuator-predicted 10-year survival, indicating greater benefit among patients with poorer baseline prognoses. Pts in the highest Sarcuator-predicted survival quartile (pOS >69%) had a mean 5-year OS benefit of 5.9% (95%CI: 3.5%-9.0%), with 63% achieving ≥5% benefit. In contrast, pts in the lowest predicted survival quartile (pOS <46%) had a mean benefit of 8.7% (95%CI: 5.3%-10.4%), with 98% achieving ≥5% benefit. Benefits varied by histology (undifferentiated pleomorphic sarcoma = 6.6%, leiomyosarcoma = 7.2%, synovial sarcoma = 8.3%, malignant peripheral nerve sheath tumor = 8.9%) and, within each subtype, was inversely correlated with Sarcuator-predicted survival. **Conclusions:** Individualized counterfactual prediction reveals substantial heterogeneity in the absolute benefit of chemotherapy in high-risk localized etSTS, driven by baseline prognostic risk and histology. This framework provides clinically relevant, patient-centered estimates that support risk-adaptive decision-making and clarify chemotherapy benefits across risk groups beyond average trial effects. Research Sponsor: None.

Sintilimab (PD-1 antibody) plus gemcitabine and docetaxel (GT) as first-line or later-line therapy in patients with advanced epithelioid sarcoma: A prospective, multicenter, single-arm, phase II clinical study.

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Background: Advanced epithelioid sarcoma (ES) responds poorly to conventional chemotherapy, with an objective response rate (ORR) of 15–27% and a median progression-free survival (mPFS) of only 4–6 months, highlighting the urgent need for new therapeutic strategies. This study aims to evaluate the efficacy and safety of Sintilimab (An approved PD-1 antibody) plus the gemcitabine and docetaxel (GT) in patients with advanced ES that has not been treated by chemotherapy. **Methods:** This is a single-arm, prospective phase II study conducted in China (ChiCTR2500095527). Patients received Sintilimab (200mg, d1, q3w) combined with gemcitabine (1000mg/m², d1,8, q3w) and docetaxel (70mg/m², d8, q3w) for up to 6 cycles, followed by Sintilimab maintenance for up to 2 years or until disease progression, intolerable adverse reactions or death. The primary endpoint was ORR, and secondary endpoints included PFS, overall survival (OS), and safety. Additionally, tumor tissue and/or blood samples were collected from patients before treatment and at the time of progression for exploratory biomarker analysis. **Results:** Between October 2024 and January 2026, Of the 19 planned patients, 16 eligible patients were enrolled. The median age was 36 years (range: 22–61), with 5 males and 11 females. All patients had metastatic or unresectable locally advanced disease (ECOG performance status 0: 12.5%; stage IV: 75.0%). With the cutoff date of January 15, 2026, 14 patients were evaluated, the median follow-up time was 8.6 months (range, 2.9 to 14.6 months), the objective response rate (ORR) was 35.71% (5/14), all of them were partial responses (PR), and the disease control rate (DCR) was 100% (14/14). The median PFS and OS were not reached. Treatment-related adverse events (TRAEs) occurred in all patients, with grade ≥ 3 TRAEs observed in 4 (28.57%) patients, included two case of neutropenia, and one case each of thrombocytopenia and transaminase elevation. **Conclusions:** The combination of Sintilimab and GT demonstrated promising efficacy in chemotherapy-naïve patients with advanced ES, achieving an ORR of 35.71% and a remarkably high DCR. Despite limited follow-up, the preliminary PFS data suggest a potential benefit from PD-1 immunotherapy. The combination showed a manageable safety profile with no new safety signals identified. Clinical trial information: ChiCTR2500095527. Research Sponsor: None.

Preliminary results of pegylated liposomal doxorubicin, dacarbazine, and toripalimab in patients with advanced primary cardiac sarcoma: An interim analysis.

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Background: Primary cardiac sarcoma (PCS) is an ultra-rare malignancy with a dismal prognosis, with previously reported median overall survival (OS) of 8–17.2 months. The roles of chemotherapy and immunotherapy remain controversial, and prospective evidence is scarce. We conducted a prospective, single-arm study to evaluate the efficacy and safety of pegylated liposomal doxorubicin (PLD), dacarbazine (DTIC), and toripalimab in patients with advanced PCS (DART-PCS). **Methods:** Patients with locally advanced or metastatic PCS were enrolled from January 2024. Treatment consisted of PLD (35–40 mg/m²) and DTIC (1.0–1.2 g/m²), each administered either on day 1 or divided over days 1–2, plus toripalimab (240 mg, day 1), every 3 weeks for six cycles. Tumor responses were assessed every two cycles by CT or MRI. Patients without progression after six cycles underwent multidisciplinary evaluation to determine further combination therapy or immunotherapy maintenance. The primary endpoint was investigator-assessed overall response rate (ORR) per RECIST v1.1. Secondary endpoints included progression-free survival (PFS), OS, and safety. Adverse events (AEs) were graded using CTCAE v5.0. Survival outcomes were estimated using the Kaplan–Meier method. The planned sample size was 30 patients. **Results:** To data cutoff, a total of 20 patients were enrolled (65% male; median age: 36 years). ECOG performance status was 0 in 30%, 1 in 45%, and 2 in 25% of patients. Eighteen patients (90%) had undergone prior surgical resection, although R0 resection was achieved in only 25%. Histologies included angiosarcoma (85%), pleomorphic undifferentiated sarcoma (10%), and epithelioid hemangioendothelioma (5%). All tumors originated in the atrium, with right atrial involvement in 85% and left atrial involvement in 15%. At enrollment, 12 patients (60%) presented with metastatic disease, and 8 (40%) had local recurrence. Responses were evaluable in 18 patients. The ORR was 44.4%, including 3 complete and 5 partial responses. The median duration of response was 21.8 weeks (95%CI: 11.7–32.0). As of January 15, 2026, the median PFS was 23.1 weeks (95%CI: 18.21–29.22), and the median OS 55.0 weeks (95%CI: 37.21–72.78). The 1-year OS rate was 54%. Treatment-related adverse events (TRAEs) occurred in all patients, with grade ≥3 TRAEs observed in 18 (90%) patients, most commonly neutropenia (90%), leucopenia (40%) and anemia (30%). One fatal serious AE (hemoptysis) was reported. The median cumulative PLD dose was 221.6 mg/m² (range: 69.0–465.1). No clinically significant cardiac dysfunction were observed. **Conclusions:** Preliminary results from the DART-PCS trial demonstrate promising antitumor activity and an acceptable safety profile for PLD, DTIC, and toripalimab in patients with advanced PCS. Further validation is warranted upon completion of the study. Clinical trial information: ChiCTR2400084334. Research Sponsor: None.

Impact of modern systemic and multimodality treatments on post-relapse survival in retroperitoneal soft-tissue sarcoma: A digital-twin target trial emulation study.

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Background: We previously observed a significant improvement in post-relapse overall survival (OS) in patients with recurrent retroperitoneal soft-tissue sarcoma (RPS) treated in 2012–2021 compared with 2002–2011. This study aimed to determine whether this survival benefit reflects advances in post-relapse treatment strategies, using digital twins to isolate the impact of systemic therapy and multimodality care. **Methods:** Adults with resected RPS and first documented recurrence were grouped by era (pre-2012 vs post-2012). Post-recurrence management was modeled as time-dependent multimodal treatment to account for treatment timing and avoid time-related bias, including repeat surgery, radiotherapy, and systemic therapy (up to five sequential lines). Detailed treatment data (surgery, radiotherapy, number of systemic therapy lines, and use of novel agents available since 2012, within or outside clinical trials) were captured. A Cox model for post-relapse survival was fitted in the post-2012 cohort using baseline covariates and time-dependent treatments. This model was used to predict the counterfactual post-relapse survival on the Monte-Carlo simulated digital-twin trajectories for pre-2012 patients under post-2012 management. The effect of post-2012 systemic therapies was isolated and applied to the pre-2012 cohort to estimate their counterfactual impact. Restricted mean survival time (RMST) at 2 and 5 years was standardized to the pre-2012 baseline distribution. **Results:** Among 872 operated patients, 417 developed recurrence; complete data were available for 86 pre-2012 and 263 post-2012 patients. Post-relapse OS significantly improved over time, with median post-relapse OS of 14.9 months pre-2012 versus 43.8 months post-2012. Observed RMST differences favored the post-2012 cohort by +5.6 months at 2 years, and +18.0 at 5 years ($p < 0.001$). Counterfactual simulation predicted that applying post-2012 management to pre-2012 patients would increase median OS to 33.8 months and RMST by +4.8 and +12.2 months at 2 and 5 years, respectively. Isolating systemic therapy alone reduced the gain by –2.2, and –5.7 months, indicating a partial but not exclusive contribution of systemic treatment advances ($p < 0.001$). **Conclusions:** Digital-twin target trial emulation suggests that post-2012 management strategies explain most of the early and a substantial portion of the long-term survival improvement after RPS recurrence. Advances in systemic therapy contribute meaningfully but do not fully explain the observed OS gains, supporting the importance of integrated multimodality post-relapse care. Research Sponsor: None.

Real-world outcomes of doxorubicin and paclitaxel in advanced Kaposi sarcoma: A TriNetX retrospective cohort study.

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Background: For decades, pegylated liposomal doxorubicin (PLD) and paclitaxel have been standard antineoplastic therapies for advanced Kaposi sarcoma (KS). However, contemporary estimates of their efficacies remain limited. This limit is particularly profound in HIV-associated KS, where advances in antiretroviral therapy and supportive care reduce the relevance of historical outcomes. **Methods:** In January 2026, the TriNetX database (171 global healthcare organizations) was queried to identify patients with KS (ICD-10-CM code C46 and ICD-O-3 code 9140/3) who received doxorubicin or paclitaxel since 2010. Patients with a history of lymphoma, cervical cancer, anal cancer, or solid organ transplantation were excluded. We extracted demographics, overall survival (OS), and time to next-line treatment or death (TTNT-D) to obtain estimated progression-free survival (ePFS). Outcomes were measured from index treatment initiation (first recorded receipt of doxorubicin or paclitaxel after KS diagnosis). Lastly, HIV-based subgroup analyses were conducted with 1:1 propensity matching by age, sex, race, and prior antineoplastic treatments. Kaplan-Meier analysis was done with significance set at $p < 0.05$. **Results:** We analyzed 935 KS patients treated with doxorubicin (including PLD) and 379 treated with paclitaxel. The patients treated with doxorubicin (median age: 45 years, 81.0% male, 48.3% HIV+) had 2- and 5-year OS of 77.5% and 70.0% and ePFS of 63.0% and 56.36% respectively. The patients treated with paclitaxel (median age: 50 years, 78.5% male, 42.7% HIV+) had 2- and 5-year OS of 71.3% and 62.4% and ePFS of 53.8% and 45.1% respectively. Within the doxorubicin cohort, HIV+ patients were younger (median age 40 vs 56 years), more often male (95.0% vs 64.7%), and had higher proportions of African American and Hispanic patients (36.4% and 14.7% vs 12.3% and 7.1%). A matched analysis of HIV+ vs. HIV- patients showed 2-year OS of 86.2% vs 71.7% ($p = 0.003$) and 2-year ePFS of 74.85% vs 52.19% ($p < 0.0001$). Within the paclitaxel cohort, HIV+ patients were also younger (median age 40 vs 64 years), more often male (96.5% vs 63.8%), and had higher proportions of African American and Hispanic patients (39.3% and 15.0% vs 9.0% and 5.0%). A matched analysis of HIV+ vs. HIV- patients showed 2-year OS of 60.3% vs 74.1% ($p = 0.151$) and 2-year ePFS of 38.0% vs 57.7% ($p = 0.023$). A matched analysis of doxorubicin vs. paclitaxel in HIV+ patients showed 2-year OS of 86.9% vs 73.0% ($p = 0.007$) and ePFS of 77.7% vs 67.9% ($p = 0.069$). **Conclusions:** This large real-world analysis provides a contemporary assessment of doxorubicin and paclitaxel in advanced KS. HIV+ status was associated with higher OS and ePFS in the doxorubicin cohort, whereas HIV- status was associated with higher ePFS in the paclitaxel cohort. Limitations include the retrospective design and imperfect reliability of TTNT-D as a surrogate for PFS. Research Sponsor: None.

Phase I trial of combination gemcitabine (gem) and nab-sirolimus (nab-S) in advanced leiomyosarcomas (LMS) or advanced soft-tissue sarcomas (STS) with *TSC1/2* alterations: Preliminary results.

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Background: Advanced LMS has limited effective therapies, with gem-based regimens being the most prescribed. Preclinical data suggest gemcitabine induces activation of the PI3K-mTOR pathway, supporting combination strategies with mTOR inhibition. Nab-S is a nano-particle albumin-bound, IV formulation of sirolimus and has demonstrated greater intra-tumoral accumulation and antitumor activity in preclinical models compared to conventional mTOR inhibitors. **Methods:** This investigator-initiated, single-center phase I study evaluates gem (900mg/m²) plus nab-s (dose levels [DL]: DL1=75mg/m² or DL2=100mg/m²) in patients (pts) using a Bayesian optimal interval (BOIN) design. Primary objective was to estimate the maximum tolerated dose (MTD) of the combination based on cycle 1 dose-limiting toxicities (DLT). Secondary objectives were to estimate objective response rate (ORR), progression-free survival (PFS), and overall survival (OS). Responses were assessed by RECIST1.1 and adverse events (AE) graded per CTCAEv5. **Results:** As of 01/22/26, all 12 pts initially planned for accrual have completed the DLT period. The original dosing schedule consisted of drug administration on Days 1 and 8 of a 21-day cycle. After the first 6 pts were enrolled, the protocol was amended to administer drugs on Days 1 and 15 of a 28-day cycle. This modification was implemented for all pts due to hematologic toxicities. While expected based on the known safety profile of nab-s and of gem, this frequently prevented Day 8 administration under the original schedule. All pts had advanced LMS, 10 pts were female and 7 had uterine LMS, the median age at time of consent was 55 yo. Three pts were included at DL1, and there was no DLT. DL2 included 9 pts: only one pt experienced a DLT of mucositis and diarrhea grade (Gr) 3 lasting for 3 days. The most frequent treatment-related Gr3-4 AE was thrombocytopenia. One pt had Gr3 pneumonitis attributed to gem and discontinued trial after 2 cycles. There was no other concern for safety. Ten pts were evaluable for response (1 pt died of disease and 1 pt chose to discontinue the trial before their first evaluation). ORR is 30% (n=3/10) at time of data cutoff and 90% pt had clinical benefit: 6 pts had stable disease with 5 pts experiencing shrinkage of disease (range: -8% to -21%) and 1 pt with 0% change. Only 1 pt had progressive disease as best response. With a median follow-up of 4 months (mo) for PFS, the median PFS (95% confidence interval [CI]) is 8.38 (1.68, not reached) mo, the 3-mo PFS (95% CI) is 78% (36%,94%), and the 6-mo PFS (95% CI) is 58% (16%,85%). With a median follow-up of 5.8 mo for OS, the 6-mo OS (95% CI) is 80% (39%,95%). **Conclusions:** The MTD was determined to be gem 900mg/m² with nab-s 100mg/m² on Days 1 and 15 of a 28-day cycle. Based on this preliminary safety and efficacy, an expansion with an additional 6 pts at this DL is ongoing. Clinical trial information: NCT06308419. Research Sponsor: Aadi Bioscience.

Efficacy and safety analysis of intraoperative radiotherapy for soft tissue sarcoma: The largest-sample, single-center, real-world data review.

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Background: This study aimed to evaluate the efficacy and safety of surgery combined with intraoperative radiotherapy (IORT) versus surgery combined with postoperative adjuvant radiotherapy in the treatment of soft tissue sarcoma (STS). It sought to identify patient subgroups that derive the most benefit from IORT and to provide evidence for treatment selection.

Methods: This retrospective single-center study was conducted at Tianjin Medical University Cancer Institute & Hospital between May 2021 and December 2024. A total of 420 patients with pathologically confirmed STS were initially screened. After applying strict inclusion and exclusion criteria, 252 eligible patients were enrolled and divided into two groups: 147 patients who underwent surgery combined with IORT using the INTRABEAM 600 System, and 105 patients who received surgery combined with conventional postoperative adjuvant radiotherapy. **Results:** After a median follow-up period of 17.2 months (range: 4.8–47.18 months), the IORT group demonstrated significantly superior outcomes. Multivariate analysis identified three independent risk factors for RFS: radiotherapy modality (IORT vs. postoperative radiotherapy, $p = 0.001$), primary versus recurrent tumor status ($p < 0.001$), and T stage ($p = 0.003$). The RFS in the IORT group was significantly better than in the postoperative radiotherapy group ($P = 0.001$). Subgroup analysis revealed that IORT was particularly advantageous for specific patient populations. Tumor size was a critical determinant: for lesions larger than 5 cm in diameter, IORT significantly improved RFS across all subgroups (> 15 cm: $p = 0.008$; 10–15 cm: $p = 0.008$; 5–10 cm: $p = 0.004$). However, for tumors smaller than 5 cm, no significant difference was observed between the two treatment modalities ($p = 0.874$). For OS, multivariate analysis identified radiotherapy type ($p = 0.01$) and AJCC stage ($p = 0.007$) as independent risk factors. The IORT group showed a trend toward improved OS, though longer follow-up is needed for definitive conclusions. The safety analysis strongly favored IORT. The incidence of treatment-related adverse events was significantly lower in the IORT group across all categories. **Conclusions:** This large-sample, single-center real-world study demonstrates that surgery combined with intraoperative radiotherapy significantly prolongs recurrence-free survival and improves local control in soft tissue sarcoma patients compared to surgery combined with postoperative radiotherapy. The benefits are most pronounced in patients with primary or recurrent tumors larger than 5 cm in diameter. Additionally, IORT offers a substantially more favorable safety profile with significantly reduced rates of radiation-related adverse events. Research Sponsor: None.

Secondary genomic alterations and clinical outcomes in myxoid liposarcoma: A multi-institutional analysis.

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Background: Myxoid liposarcoma (MLS) is defined by *DDIT3* rearrangements. The clinical and prognostic significance of secondary genomic alterations remains incompletely characterized. We retrospectively evaluated the clinical, pathological, and prognostic implications of commonly co-occurring mutations in patients with MLS. **Methods:** Patients with pathologically confirmed MLS treated at Memorial Sloan-Kettering Cancer Center (MSKCC) and MD Anderson Cancer Center (MDACC) who underwent next-generation sequencing (NGS) on the primary tumor (9/2010–5/2024) were included. To ensure the analysis represented *de novo* mutations rather than acquired alterations, patients with NGS performed only at the time of recurrent disease were excluded. The primary endpoint was disease-free survival (DFS) among surgically treated patients. Associations between genomic alterations and clinico-pathologic characteristics were assessed using univariable and multivariable analyses. **Results:** The cohort included 76 patients (67 MSKCC, 9 MDACC) with a median age of 39 years. At diagnosis, 83% of patients ($n = 63$) had localized disease and underwent definitive surgery, while 17% presented with *de novo* metastasis; 45% had high-grade disease ($\geq 5\%$ round cell component). Genomic analysis identified *TERT* promoter mutations in 68%, *PIK3CA* in 30%, and *PTEN* in 18%. Notably, *PIK3CA* and *PTEN* mutations were not mutually exclusive, with 10.5% of the total cohort harboring concurrent alterations in both genes. *TERT* promoter mutations were significantly associated with male sex (75% vs 33%, $p < 0.001$), older age (40 vs 33 years, $p = 0.02$), high-grade pathology (54% vs 25%, $p = 0.026$), and larger median tumor size (12.9 vs 7.5 cm, $p = 0.002$). *PIK3CA* mutations were associated with male sex (83% vs 53%, $p = 0.02$) and a trend toward larger median tumor size (13.6 vs 9.3 cm, $p = 0.061$) and *de novo* metastasis (30% vs 11%, $p = 0.053$). For the 63 patients with localized disease, the median DFS was not reached (95% CI: 55.7–NR) with a 24-month DFS rate of 75% (95% CI 61–84). In univariable analysis for DFS, significant predictors of recurrence included *PIK3CA* mutation (HR 4.61; $p = 0.001$), *PTEN* mutation (HR 5.15; $p < 0.001$), tumor size (HR 1.06 per cm; $p = 0.012$), high-grade pathology (HR 2.81; $p = 0.024$) and male sex (HR 2.79; $p = 0.049$). The presence of both *PIK3CA* and *PTEN* mutations conferred particularly poor prognosis (HR 16.34 compared to neither mutation; $p < 0.001$). In separate multivariable analyses adjusted for grade, both *PIK3CA* (HR 5.75, $p < 0.001$) and *PTEN* (HR 4.27, $p = 0.002$) remained independent predictors of DFS. **Conclusions:** Secondary genomic alterations in MLS are highly prevalent and connote distinct clinical phenotypes. While *TERT* promoter mutations correlate with aggressive pathologic features, *PIK3CA* and *PTEN* mutations are independent prognostic factors for DFS and may help risk-stratify patients for potential adjuvant therapies. Research Sponsor: Cancer Center Support Grant; P30 CA008748.

Integrating personalized ctDNA into clinical surveillance of soft tissue sarcoma: Performance, timing, and histologic insights.

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Background: Soft tissue sarcoma (STS), particularly larger and biologically aggressive subtypes, carries a high risk of relapse making effective post-operative surveillance essential. CtDNA utility in STS remains elusive. **Methods:** We conducted a retrospective review of STS who underwent surgical resection and post-operative surveillance with serial personalized ctDNA testing (Signatera) and cross-sectional imaging between April 2023– January 2026. Diagnostic performance was assessed by sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV), using imaging-confirmed progression as the reference standard. Subgroup analyses by major histologic subtype conducted. Detection times were referenced to surgery, and lead time was summarized using medians and interquartile ranges (IQR). Paired detection times were compared using the Wilcoxon signed-rank test, with Mann–Whitney U test as a sensitivity analysis. **Results:** Total 114 patients with ctDNA samples were screened. 101 patients with paired ctDNA (total 1,005 plasma samples) and imaging surveillance were included. The median age at diagnosis was 53 years, and the cohort was evenly distributed by sex (50.5% male, 49.5% female). Most patients were White (86.1%), 13.9% African American; 58.4% identified as non-Hispanic and 40.6% as Hispanic. Using imaging as the reference standard, 33 patients developed radiographic progression. ctDNA was positive in 27, yielding a sensitivity of 81.8% (95% CI, 65.6%–91.4%). Among 68 patients without progression, 66 remained ctDNA negative, corresponding to a specificity of 97.1% (95% CI, 89.9%–99.2%). The PPV and NPV were 93.1% and 91.7%, respectively. Six patients (18.2%) had radiographic progression despite persistently negative ctDNA, forming a clinically relevant discordant subgroup. Among patients with paired molecular and radiographic progression (n = 27), ctDNA detected progression earlier in 44%, while imaging led in 56%. Overall detection timing did not differ significantly between modalities (median lead time, –0.21 months; IQR, –1.42 to 1.67; p = 0.91). Tumors associated with ctDNA positivity were numerically larger than ctDNA-negative (median, 8.75 cm vs 7.0 cm, p = 0.051). CtDNA detection dynamics varied by histologic subtype, with a nonsignificant numerical trend toward earlier detection in synovial sarcoma. The most common site of metastatic involvement was lung (40%), followed by liver (20%). **Conclusions:** Personalized ctDNA surveillance showed high specificity and strong diagnostic performance in STS and detected progression earlier than imaging in a subset of patients, though no overall lead-time advantage was observed. Histology-specific differences suggest biologic variability in ctDNA detectability and support prospective, subtype-focused studies to define optimal integration with imaging. Research Sponsor: None.

Percutaneous cryoablation for the treatment of extra-abdominal desmoid tumors.

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Background: Management of extra-abdominal desmoid tumors (DT) has evolved over the last decade, with emphasis on conservative management based on guidelines from the Desmoid Tumor Working Group. There is growing evidence for ablative therapies, including percutaneous cryoablation (PCA), but there is little data on long-term outcomes with PCA. This large cohort study reports efficacy and long-term outcomes for patients with extra-abdominal DTs with PCA. **Methods:** Patients with pathologically-confirmed extra-abdominal DT were recruited consecutively at a high-volume referral center from 2014-2025. Data points including patient demographics, tumor characteristics, and procedural details for cryoablation were collected. The primary outcome was ablation success using the modified response criteria in solid tumors (mRECIST), measuring change in viable tumor along the longest tumor diameter. Secondary outcomes were change in lesion volume (TLV), complications per Clavien-Dindo classification, patient-reported symptom resolution, and progression-free survival (PFS). **Results:** A total of 53 patients undergoing 83 PCA procedures were identified. 67.9% of patients were female. The median follow up time was 40.1 months. Thirty-two patients were treated with PCA as first-line therapy, while 21 were treated as salvage therapy. The median change in viable tumor volume using mRECIST was -100%; 26 patients had a complete response (CR), 13 had partial response (PR), 7 had stable disease (SD), and 13 had progressive disease (PD). The median change in TLV was -71.7%. One-year and five-year PFS rates were 88.2% and 66.6% respectively. Fifty patients had symptoms including pain, an enlarging mass, or decreased range of motion prior to PCA; 94.0% had symptomatic improvement or resolution after PCA. Two patients had major complications: one inferior epigastric hemorrhage and one small bowel injury treated with a small bowel resection. **Conclusions:** This study provides the largest cohort of extra-abdominal desmoid tumors undergoing PCA. PCA can lead to patient-reported symptom resolution, a substantial decrease in mRECIST and TLV, and has a low complication rate. This study adds further evidence that PCA is safe and effective for treating extra-abdominal desmoid tumors. Research Sponsor: None.

Investigating the molecular characteristics underlying desmoid tumor clinical trajectory.

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Background: Desmoid tumors are locally aggressive mesenchymal neoplasms that primarily affect adolescents and young adults. They demonstrate a range of clinical behavior from spontaneous regression to refractory growth leading to morbidity and sometimes mortality. However, there are no prognostic biomarkers for patients with desmoid tumors and we have a limited understanding of the biology behind the range of clinical behavior. Thus, we aimed to characterize the clinical course of patients with banked desmoid tumors at our institution from across the age spectrum, and correlate clinical behavior with genetic alterations and gene expression signatures. **Methods:** We identified 64 adult patients through our adult sarcoma biobank and 5 patients through our pediatric biobank with desmoid fibromatosis and banked samples. Retrospective chart review was conducted including patient characteristics, disease features, treatment course, and outcomes. Genetic analysis was completed on 61 patients (43 targeted exome sequencing, OncoPanel). To characterize gene expression, we performed single nucleus RNA sequencing (snRNAseq) on 15 samples from 12 patients, with concurrent *CTNNB1* genotyping to accurately identify tumor cells. Primary analyses included cell annotation of clusters and differential gene expression between progressing and stable/regressing tumors. **Results:** A total of 69 patients were included in this study. Median age at diagnosis was 35 years (range 2–83), with 68% female. Median tumor size at diagnosis was 5.2cm (range 0.7–25.0). Tumor location included abdominal wall (41%), mesenteric (25%), trunk/breast (14%), extremity (16%), and head/neck (5%). At time of tissue collection 39% of tumors were progressing, 23% were stable, and 10% were regressing (28% unknown). Among 61 sequenced tumors, 72% and 21% harbored *CTNNB1* and *APC* mutations, respectively, and 7% showed no mutations in either gene. snRNAseq resulted in a dataset of over 180,000 high-quality nuclei. Cell composition differences were identified across the spectrum of disease states. Concurrent single-nucleus *CTNNB1* genotyping revealed expression differences in the tumor cell compartment between progressing and non-progressing tumors, including collagen/extracellular matrix proteins and mesenchymal transcription factors. **Conclusions:** In this cohort of adult and pediatric desmoid tumors, integration of clinical annotation and molecular characteristics identified gene expression programs associated with tumor progression. These findings provide new insights into the biology underlying variable clinical trajectory in desmoid tumors, implicating altered collagen/extracellular matrix and mesenchymal transcription factor programs. Ongoing bulk RNA sequencing and immunohistochemical analyses are being performed to assess the potential of these signatures as predictive biomarkers and therapeutic targets. Research Sponsor: Desmoid Tumor Research Foundation.

Phase II pilot study of pembrolizumab (PEM) and neoadjuvant radiation therapy (nRT) in high-risk soft tissue sarcomas (STS).

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Background: Pathologic necrosis (PN) after neoadjuvant therapy in STS has been associated with improved outcomes. We investigated clinicopathologic outcomes of concurrent PEM/nRT in STS. **Methods:** Adults with localized STS [FNCLCC grade 3 (> 1.5 cm) or grade 2 (> 3 cm)] received 3 doses of PEM (200 mg IV q21 d) concurrently with nRT, followed by surgery. Primary endpoint was the rate of post-treatment complete pathologic necrosis (CPN; $\geq 90\%$ PN). 26 subjects provided 94% power to detect an increase in CPN rate from 15% to 40%; ≥ 7 cases with CPN would exclude a 15% CPN rate. Secondary endpoints included toxicity (CTCAE 5.0), response (RECIST 1.1), and event-free survival (EFS). **Results:** 27 STS patients were enrolled including UPS (10; 37%), DD liposarcoma (8; 30%), myxofibrosarcoma (2; 7%), solitary fibrous tumor (2; 7%), and other STS (5; 19%). 26 patients were evaluable for CPN and 25 for EFS. All except 2 (7%) received 3 planned PEM doses. All completed planned RT (50–50.4 Gy). 2 (7%) with UPS had partial responses prior to surgery. Median tumor size was 10 cm (range 2.1–26 cm). R0 resection was achieved in 92%. 14 (54%) patients had grade 3 tumors; 12 (46%) had grade ≥ 2 . Median post-treatment PN was 55% (range 0–99%) with 5/26 (19%) having CPN. Median follow-up time was 33.4 months (m) from PEM initiation (range 1.6–60 m). 12/25 patients had an EFS event. Among all patients (n = 27), 12 developed only distant metastatic disease, and 1 developed local and distant recurrence. AEs were consistent with anticipated effects of PEM and RT. Two grade 5 events occurred (ischemic colitis, prostate cancer), both judged unrelated to study therapy. 3 patients experienced wound dehiscence, and one had wound infection. EFS at 12 m was 68%; at 57.5 m, it was 52%. Post-treatment PN as a continuous variable was inversely associated with EFS (HR = 22.47, p = 0.004). Increased tumor size was also associated with inferior EFS (HR = 1.09/cm, p = 0.04). In multivariable analyses, both necrosis and tumor size remained independently associated with EFS (HR = 26.52 and 1.09, p = 0.004 and 0.041, respectively). Sex, age, histology, tumor grade/location, and radiation modality were not associated with EFS. **Conclusions:** PEM did not increase the proportion of patients with post-treatment CPN after RT. Unexpectedly, increased tumoral necrosis after treatment was associated with inferior EFS. It is possible that increased post-treatment tumoral necrosis may identify a subset of STS patients less likely to benefit from PEM/nRT or who have inherently more aggressive tumor biology. These findings warrant additional studies for validation and exploration of the mechanisms and clinical applications of these findings. PN after PEM/nRT might provide a readily available biomarker that could be used to adjust therapy in those unlikely to benefit from PEM/nRT. Correlative analysis using pre- and post-treatment tumor are on-going and will be presented. Clinical trial information: NCT03338959. Research Sponsor: Merck.

Neoadjuvant versus adjuvant chemotherapy for resectable high-grade soft tissue sarcoma: A real-world propensity-matched survival analysis.

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Background: High-grade soft tissue sarcomas are aggressive malignancies for which complete surgical resection remains the cornerstone of curative-intent therapy. Current clinical guidelines recommend consideration of perioperative chemotherapy for selected high-risk patients; however, the optimal timing of systemic therapy remains uncertain. We performed a real-world analysis to compare survival outcomes between neoadjuvant and adjuvant chemotherapy in patients with resected high-grade soft tissue sarcoma. **Methods:** We conducted a retrospective cohort study using the TriNetX Database, identifying adults (≥ 18 years) with high-grade soft tissue sarcoma who underwent surgical resection and received combination chemotherapy with doxorubicin and ifosfamide either within 6 months before surgery or after surgery. The index date was defined as time of diagnosis. Propensity score matching (1:1) was performed to balance baseline demographics and various comorbidities. Overall survival (OS) was assessed using Kaplan–Meier methods and Cox proportional hazards models at fixed time points (1, 3, 5, and 10 years) and over the entire follow-up period. **Results:** A total of 714 patients were identified (479 adjuvant; 235 neoadjuvant). After propensity score matching, 229 patients were included in each cohort. At 1 year, overall survival was similar between adjuvant and neoadjuvant chemotherapy (53.1% vs 53.1%; risk ratio [RR] 1.06, 95% CI 0.81–1.37; log-rank $p = 0.77$). Additionally, analyses at 3, 5, and 10 years demonstrated no statistically significant differences in OS between cohorts, with overlapping Kaplan–Meier survival curves at all evaluated time points. Over the entire follow-up period, survival probabilities at the end of follow-up were 51.5% in the adjuvant cohort and 53.4% in the neoadjuvant cohort. There was no significant difference in overall survival (hazard ratio [HR] 1.04, 95% CI 0.75–1.44; $p = 0.73$). **Conclusions:** In this large, real-world, propensity-matched analysis of patients with resectable high-grade soft tissue sarcoma, survival outcomes were comparable across short-, intermediate-, and long-term follow-up intervals in both neo-adjuvant and adjuvant chemotherapy cohorts. Current guidelines recommend neo-adjuvant radiation treatment as category 1, and chemotherapy (neo-adjuvant or adjuvant) is a consideration. Neo-adjuvant chemotherapy has the potential to delay definitive treatment, however, this analysis suggests that the timing of chemotherapy does not adversely impact the outcomes in short or long term follow up. There are several limitations to our analysis (size of the tumors and grading was not available and timing of XRT could not be assessed, however, given that AIM chemo cohort was selected, it can be assumed that patients had higher grade, larger tumors and received XRT as standard of care. Research Sponsor: None.

A phase 1b study of tegavivint, a TBL1 inhibitor, with gemcitabine in patients with relapsed or refractory osteosarcoma (TIGER).

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Background: The Wnt-signaling pathway and its downstream transcriptional effector, β -catenin, are dysregulated in osteosarcoma (OS), promoting tumor growth and metastatic spread. When the Wnt pathway is activated, transduction beta-like protein 1 (TBL1) binds nuclear β -catenin, forming a complex that is necessary to dock on the promoters of Wnt-driven genes. Tegavivint is a first-in-class small molecule inhibitor that selectively binds TBL1, inhibiting TBL1- β -catenin complex formation, and resulting in the nuclear degradation of β -catenin and inhibition of oncogenic transcriptional activation. Preclinical testing of *in vivo* OS models demonstrates that tegavivint reduces tumor volume and suppresses lung metastases, and has additive effects when combined with gemcitabine. In a phase 1 trial conducted by the Children's Oncology Group, the recommended phase 2 dose (RP2D) of tegavivint was determined to be 6.5 mg/kg administered intravenously (IV) on a 3 weeks on/1 week off schedule, with no maximum tolerated dose (MTD) determined. The primary objective of this phase 1b study is to define the MTD and/or RP2D of tegavivint combined with gemcitabine, including assessment of toxicities and preliminary efficacy, in patients with relapsed or refractory (r/r) OS. **Methods:** TIGER is a phase 1b, multi-center, dose escalation trial assessing tegavivint combined with gemcitabine in patients with r/r OS. Eligible patients will be 1-30 years of age with either measurable or evaluable disease per RECIST v1.1 who have fully recovered from the clinically significant acute effects of prior therapy and have adequate organ function. Prior treatment with gemcitabine is allowed. Patients with active CNS disease, recent bisphosphonate treatment, metabolic bone disease or disorder, uncorrected hypocalcemia or low vitamin D, and prior receipt of tegavivint are excluded. Patients will receive tegavivint IV at the dose level assigned at study entry on days 1, 8, and 15 and gemcitabine at a fixed dose of 1000 mg/m² IV on days 1 and 8 of a 21-day cycle. Patients may receive up to 17 cycles provided they do not experience disease progression or unacceptable toxicity. Tegavivint will be dose escalated using a rolling six design to test two planned dose levels, 5 mg/kg [dose level (DL) 1] and 6.5 mg/kg (DL 2), with dose de-escalation to 3 mg/kg (DL 0) if needed. An additional 6 patients will be enrolled to a dose expansion cohort at the MTD/RP2D to obtain additional pharmacokinetic (PK), safety, and preliminary efficacy data. Peripheral blood for correlative studies will be obtained at serial timepoints to conduct PK studies, pharmacodynamic testing of serum protein biomarkers associated with β -catenin inhibition, and analysis of ctDNA and circulating tumor cells. Tumor tissue will be analyzed for TBL1 and Wnt/ β -catenin signaling (sequencing and protein expression). Clinical trial information: NCT07144254. Research Sponsor: Peach Bowl LegACY Fund; Iterion Therapeutics.

A phase 1/2, multi-center, open-label study to evaluate the safety, tolerability, pharmacokinetics, radiation dosimetry, and preliminary anti-neoplastic activity of LNTH-2403, a LRRC15-targeted ¹⁷⁷lutetium-labeled monoclonal antibody, in patients with relapsed/refractory osteosarcoma.

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Background: Treatment for relapsed and refractory (R/R) osteosarcoma (OST) has not changed for decades. R/R OST has a poor prognosis with a 12% 4-month event-free survival (EFS). Leucine-Rich Repeat Containing 15 (LRRC15) is a type I transmembrane protein on OST cells and cancer associated fibroblasts. Approximately 90% of OST express LRRC15; high expression predicts aggressive disease and shorter survival. LNTH-2403 is a high-affinity LRRC15-targeting fully humanized antibody with a ¹⁷⁷lutetium payload. Preclinical data show anti-tumor activity in several OST models, demonstrating LNTH-2403's potential to treat R/R OST. **Methods:** This first-in-human, multicenter, open-label phase 1/2 study will evaluate the safety, tolerability, pharmacokinetics (PK), biodistribution (BD), radiation dosimetry (RD), and preliminary anti-neoplastic activity in patients ≥ 12 years of age with LRRC15-expressing R/R OST. The primary endpoints are to identify the maximum tolerated dose (MTD; phase 1) and 4-month EFS (phase 2). LRRC15 expression by immunohistochemistry will be confirmed by a central lab; pre-screening is allowed. Initiated in Q1 2026, phase 1 will test LNTH-2403 at 30, 50, and 70 mCi/m² every 8 weeks in up to ~30 patients. A 3+3 design will be used to define the MTD and estimate the recommended phase 2 dose (RP2D). Phase 2 will evaluate LNTH-2403 at the RP2D in ~25 patients with R/R OST. Retreatment after Cycle 1 is permitted for patients who continue to meet initial eligibility requirements, have cumulative doses to target organs predicted to be below radiation tolerance limits, and whose bone marrow has recovered. Safety testing includes adverse events (AEs), serious AEs (SAEs), laboratory parameters (chemistry, hematology, coagulation, urinalysis), electrocardiograms, vital signs, and physical examinations. BD and RD are based on serial single photon emission computed tomography (SPECT)/computed tomography (CT) and planar imaging. PK data will be generated from serial blood sampling for radioactivity. Overall response rate (ORR) and EFS are defined by the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 per investigator reads. As ORR by RECIST is challenging in OST due to tumor calcification, efficacy testing also includes physiologic response by fluorine-18 (¹⁸F)-fluorodeoxyglucose (FDG)-positron emission tomography (PET)/CT whole body scans and magnetic resonance imaging of the primary site, sites of known and presumed metastases, and the chest, abdomen, and pelvis. For this open-label study, all statistical methods will be descriptive in nature with no formal statistical hypotheses. NCT07357519; Research Sponsor: Lantheus. Clinical trial information: NCT07357519. Research Sponsor: Lantheus.

StrateGIST 3: A randomized, phase 3 study of velzatinib (IDRX-42) versus sunitinib in patients with advanced gastrointestinal stromal tumors after imatinib therapy.

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Background: Most gastrointestinal stromal tumors (GISTs) are driven by mutations in *KIT*. Tyrosine kinase inhibitors (TKIs) such as imatinib and sunitinib (first- and second-line therapies for GIST, respectively) are available, but resistance can develop and is primarily mediated by additional *KIT* mutations in the ATP binding pocket (exon [ex] 13/14) and activation loop (ex 17/18). While sunitinib targets mutations in exon 13/14 in the second-line setting, it has low response rates and short progression-free survival (PFS). Therefore, there is a need for novel therapies with broad mutation coverage, and for patients (pts) with disease progression on, or intolerance to, approved therapies. Velzatinib (subject to USAN approval) is a novel, highly selective, oral *KIT* TKI that potently and selectively inhibits primary and secondary resistance *KIT* mutations. In StrateGIST 1, an ongoing, phase 1/1b study in adult pts with advanced GIST, velzatinib exhibited promising clinical activity and favorable safety in 2nd- and later-line pts at the recommended phase 3 dose of 300-mg QD tablet (or exposure-equivalent 400-mg QD capsule). As of December 15, 2025, median PFS (95% CI) was 13.7 (7.4–18.4) months and confirmed ORR (95% CI) was 33% (19.5–48.0) in 2nd-line pts (N=46) at the recommended phase 3 dose, supporting the further evaluation of velzatinib in pts with advanced GIST after progression on, or intolerance to, imatinib. **Methods:** StrateGIST 3 is a phase 3, randomized, multicenter, open-label study (NCT07218926) to evaluate velzatinib vs sunitinib in adult pts with advanced GIST after progression on or intolerance to imatinib. Recruitment for this study opened on December 3, 2025, and the total duration of the study is estimated to be approximately 5 years. Pts must have documented mutation status of *KIT* and/or *PDGFRA*, and will be excluded if they have GIST that is wild type for both *KIT* and *PDGFRA* or if they have an activating *PDGFRA* exon 18 mutation. Approximately 450 pts will be randomized (1:1) to receive either velzatinib (300-mg QD tablet, continuous dosing) or sunitinib (50 mg QD, 4 weeks on/2 weeks off). The randomization will be stratified by activating mutation (ex 11 vs ex 9 vs other) and intolerance to first-line imatinib (yes vs no). The primary endpoint is PFS according to modified RECIST for GIST (mRECIST-GIST), by blinded independent central review (BICR). The key secondary endpoint is overall survival, and additional secondary endpoints include PFS per investigator assessment, PFS-2, confirmed objective response rate per BICR and per investigator, time to response per BICR and per investigator, health-related quality of life and functioning, plasma drug concentrations, and safety and tolerability. This trial is now recruiting. This study (NCT07218926) is funded by GSK. Clinical trial information: NCT07218926. Research Sponsor: GSK.

Phase 1a/1b study of the safety, pharmacokinetics, and antitumor activity of ziftomenib in combination with imatinib in patients with advanced gastrointestinal stromal tumors (GIST) after imatinib failure.

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Background: GIST is the most common mesenchymal neoplasm of the digestive tract and is mainly driven by gain-of-function oncogenic mutations in the receptor tyrosine kinase KIT. Patients with GIST are typically treated with anti-KIT tyrosine kinase inhibitors (TKIs) such as imatinib. However, few patients achieve a complete response, and most eventually progress due to secondary *KIT* alterations that cause resistance to therapy. Other TKIs are approved in later lines but have shown only moderate clinical outcomes, highlighting the need for additional therapeutic approaches. Preclinical studies have shown that the menin-KMT2A complex epigenetically upregulates *KIT* expression in GIST cells. Ziftomenib is a potent and highly selective menin inhibitor that disrupts formation of the menin-KMT2A complex. Ziftomenib plus imatinib has demonstrated synergistic antitumor activity in imatinib-sensitive and -resistant GIST models, with reduced KIT protein levels and downstream oncogenic signaling observed in imatinib-resistant GIST patient-derived xenografts treated with the combination. Together, ziftomenib plus imatinib may enhance KIT recycling while reducing *KIT* transcription. This combination is currently being investigated clinically in patients with imatinib-sensitive and -resistant advanced GIST. **Methods:** KOMET-015 (NCT06655246) is an ongoing phase 1a/1b, open-label study to determine the safety, tolerability, recommended phase 2 dose (RP2D), and preliminary antitumor activity of ziftomenib plus imatinib (400 mg or <400 mg if previously reduced due to intolerance) for advanced/metastatic GIST. KOMET-015 includes dose-escalation, RP2D determination, and dose-expansion parts. Eligible patients (≥ 18 yrs) must have a biopsy-proven diagnosis of advanced/metastatic *KIT*-mutant GIST (T670X excluded) that progressed on imatinib (for dose-escalation and RP2D determination parts), with an ECOG PS of ≤ 2 and measurable disease per RECIST v1.1 modified for GIST (mRECIST). Dose escalation will be based on an i3+3 design to evaluate the safety and tolerability of up to 4 dose levels (with potential for additional doses) of ziftomenib combined with imatinib. Based on escalation, up to 2 dose levels will be selected for comparison to determine the RP2D. The dose-expansion part will examine the preliminary clinical activity of the RP2D in patients assigned to 1 of 3 cohorts: Cohort A: patients who progressed on imatinib as immediate prior therapy, Cohort B: patients who failed imatinib and had received ≥ 2 lines of therapy, and Cohort C: imatinib-naïve patients. Tumor response will be assessed per mRECIST. All adverse events will be recorded, monitored, and graded based on CTCAE v5.0. The trial is open and actively recruiting in the United States. Clinical trial information: NCT06655246. Research Sponsor: Kura Oncology, Inc.

Clinical feasibility of 68Ga-DOTATATE PET/CT to identify SSTR-positive soft tissue sarcoma for PRRT selection.

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Background: Soft tissue sarcomas (STS) are biologically heterogeneous with limited effective systemic options in advanced disease. While 18F-FDG PET/CT provides metabolic assessment, it does not identify actionable receptor targets. Somatostatin receptor 2 (SSTR2) is expressed in subsets of mesenchymal tumors, and SSTR-targeted imaging with 68Ga-DOTATATE PET/CT is routinely used to select patients with neuroendocrine tumors for peptide receptor radionuclide therapy (PRRT) with 177Lu-DOTATATE. Whether receptor-targeted PET screening can feasibly characterize SSTR expression across STS subtypes and support future PRRT trial design is unknown. This study evaluates the feasibility and yield of 68Ga-DOTATATE PET/CT as a screening strategy in STS. **Methods:** This is a prospective, open-label, single-center pilot study enrolling 30 adults with any-stage STS who are candidates for systemic therapy and who have undergone standard-of-care PET/CT within 30 days. Participants undergo a single 68Ga-DOTATATE digital PET/CT within 14 days of consent, acquired approximately 60 minutes post-injection with non-contrast CT for attenuation correction and anatomic localization. Quantitative metrics including SUVmax and total tumor volume are centrally derived. Optional biobanking permits pre-imaging blood collection for exploratory circulating biomarkers. Key exclusions include recent long-acting somatostatin analog use, pregnancy or lactation, acute infection, hypersensitivity to somatostatin analogs, or inability to complete imaging. The primary endpoint is screening feasibility, defined by successful scan acquisition and interpretable image quality. Secondary endpoints include lesion-level detectability, safety, and characterization of uptake patterns using modified Krenning-style criteria and quantitative PET parameters across histologic subtypes. Imaging findings may be reviewed at multidisciplinary sarcoma tumor board as part of routine clinical care, including discussion of potential PRRT eligibility, but tumor board recommendations are not study endpoints. Exploratory analyses will assess concordance between imaging findings and available tumor immunohistochemistry or circulating biomarkers. Analyses are descriptive. The planned accrual is 30 patients over approximately 24 months at a high-volume sarcoma center. Enrollment and imaging are ongoing. This study will establish the feasibility of receptor-targeted PET screening in STS and characterize the frequency and distribution of SSTR-positive disease, providing data necessary to inform the feasibility and design of subsequent 177Lu-DOTATATE interventional trials. Clinical trial information: NCT06500065. Research Sponsor: None.

SARC045: A phase 2 trial of tebentafusp in HLA-A*02:01–positive patients with advanced clear cell sarcoma.

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Background: Tebentafusp (Kimmtrak) is a first-in-class bispecific T-cell engager, specifically a T-cell receptor (TCR)–anti-CD3 fusion protein, approved for HLA-A*02:01+ metastatic or unresectable uveal melanoma. Tebentafusp binds to the HLA-A02:01/gp100 peptide complexes on the tumour cell surface, recruiting polyclonal T cells, via CD3, to release cytokines and cytolytic mediators against the tumour. Clear cell sarcoma (CCS) is an ultra-rare soft-tissue sarcoma subtype with poor prognosis and limited therapeutic options. On histopathology, CCS is characterised by the expression of melanocytic antigens, including gp100. **Methods:** This Phase 2 trial evaluates the efficacy of Tebentafusp in HLA-A*02:01 positive patients with advanced CCS. Twenty-three patients will be treated with weekly I.V. infusion of Tebentafusp at the recommended dose until evidence of clinical benefit or patient withdrawal from study. Baseline and on-treatment biopsies, as well as longitudinal peripheral blood samples will be collected for translational analyses. Prospective data will also be collected from an observational non-comparative cohort of up to 24 patients with advanced CCS not eligible for the study due to incompatible HLA. Enrolment to the study has commenced in October 2025 in the US, with two currently active sites (Memorial Sloan Kettering Cancer Center and University of Southern California). One additional US site (Northwestern University) and one UK site (The Royal Marsden Hospital) are due to open. At the time of submission, 1 HLA-A*02:01 advanced CCS patient had started treatment with Tebentafusp. Clinical trial information: NCT06942442. Research Sponsor: Immunocore.

SARC046: A phase II trial of nab-sirolimus in patients with progressing or symptomatic epithelioid hemangioendothelioma.

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Background: Epithelioid hemangioendothelioma (EHE) is an ultra-rare vascular sarcoma with about 120 cases diagnosed in the US per year. Although it is commonly considered an indolent disease, in its aggressive form clinical outcomes are poor. Molecularly, EHE is characterized by the presence of oncogenic fusions with HIPPO pathway effectors TAZ or YAP; TAZ-CAMTA1 or YAP-TFE3. YAP/TAZ are modulators of mTORC1 in preclinical models, suggesting that mTOR inhibition may be an effective treatment mechanism for EHE. Nab-sirolimus is albumin bound sirolimus, which achieves higher intratumoral accumulation compared to oral sirolimus and has demonstrated increased antitumor activity in preclinical cancer models compared to the oral mTOR inhibitors sirolimus and everolimus. This is an open label, multi-center, single arm, phase II clinical trial with a two-stage design, testing nab-sirolimus for progressing or symptomatic EHE. The primary objective is to determine ORR of nab-sirolimus in patients with EHE who require systemic treatment. We hypothesize that nab-sirolimus will have significant clinical efficacy for EHE as measured by the primary endpoint of objective response rate, as well as by secondary outcomes including progression free survival benefit over historical controls and by improvement in patient reported outcomes (PROs). If positive, this trial could lead to a new standard of care for treating EHE. **Methods:** This is a single arm, multi-center, phase 2 study with a two-stage design. Key inclusion criteria include histologically or cytologically confirmed EHE that is either progressing or clinically symptomatic, not a candidate for curative intent surgery, and requires systemic therapy in the opinion of the investigator, radiographically evaluable disease by RECIST v1.1, age ≥ 18 years, ECOG performance status ≤ 2 , and adequate end organ function. With a Simon two-stage optimal design with one sided alpha 0.10, power 90%, assuming a historical control ORR 5% to detect an ORR of 20% (alternative hypothesis), 12 patients will be included in the first stage. If there is ≥ 1 response, an additional 25 patients will be enrolled to a total of 37 patients. ≥ 4 responses are needed for a significant result. The total planned accrual is 41 patients to account for unevaluable patients who may be enrolled, 10% above the required evaluable patients. Planned post hoc subgroup analyses will include outcomes by fusion type and presence of serosal effusions at the time of study enrollment. The trial is registered at clinicaltrials.gov NCT07104331. Clinical trial information: NCT07104331. Research Sponsor: U.S. Department of Defense; HT9425-25-1-0418; Aadi Bioscience.

Investigator-initiated phase II trial of ABSK043, an oral PD-L1 inhibitor, in patients with angiogenic sarcoma.

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Background: Angiogenic sarcomas (AS) represent a group of rare mesenchymal malignancies arising from the vascular endothelium. Patients with locally advanced or metastatic disease have poor outcomes due to limited availability of effective systemic treatment options. Emerging data suggest that immune checkpoint blockade (ICB) has activity in select patients, but prospective data is lacking for ultra-rare subtypes of AS including intimal sarcoma and epithelioid hemangioendothelioma (EHE). **Methods:** This is a single institution phase II investigator-initiated open label trial of ABSK043, an oral PD-L1 inhibitor in patients with AS. The primary endpoint is objective response rate. Secondary endpoints include progression free survival, overall survival and incidence of treatment emergent adverse events. Exploratory objectives include tissue- and blood-based correlative analyses to identify molecular biomarkers associated with ICB response/resistance in AS. Key inclusion criteria include histologically proven EHE, intimal sarcoma or scalp angiosarcoma with evidence of disease progression, age ≥ 18 years, ECOG performance status 0-2, adequate organ function, and measurable disease by RECIST v1.1. Exclusion criteria include ongoing systemic immunosuppressive therapy, active autoimmune disease, prior treatment with PD-(L)1 directed therapy, untreated brain metastases, or gastrointestinal conditions that may impair oral drug absorption. Participants will receive ABSK043 800mg orally twice daily until disease progression or unacceptable toxicity. Radiologic assessments by CT or MRI will be performed every 12 weeks. Research bloods will be collected prior to treatment initiation and with radiologic assessments, and biobanked for future correlative analyses (including longitudinal ctDNA assessment). Archival tissue or a fresh biopsy will be collected during screening for all patients. Patients who achieve partial response will undergo on-treatment and post-progression biopsies for correlative analyses (including whole genome and transcriptome sequencing and multiplex immunohistochemistry). This study opened in August 2025 and is actively recruiting. Planned enrollment is 20 patients, with accrual expected to complete by June 2027. Clinical trial information: NCT07014137. Research Sponsor: Abbisko Therapeutics.

A phase Ib/II study of mirdametinib in combination with palbociclib in patients with advanced dedifferentiated liposarcoma.

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Background: Dedifferentiated liposarcoma (DDLPS) is a rare adipocytic malignancy characterized by frequent amplification of *MDM2* and *CDK4* and associated with poor outcomes, with a median overall survival of approximately 15 months. A phase II trial at Memorial Sloan Kettering Cancer Center demonstrated activity of the CDK4/6 inhibitor palbociclib in advanced WD/DDLPS, with a 12-week progression-free survival (PFS) rate of 57%, exceeding historical chemotherapy benchmarks (<35%) and leading to its inclusion in the NCCN Guidelines. Despite this, durability of benefit remains limited, and outcomes following progression are poor. Preclinical work from our group demonstrated that CDK4/6 inhibition in DDLPS induces cellular geroconversion from quiescence to irreversible senescence, accompanied by *MDM2* downregulation. This process requires suppression of HRAS signaling and inhibition of the MAPK pathway and is associated with activation of the senescence-associated secretory phenotype (SASP). Preclinical models further suggest that dual CDK4/6 and MEK inhibition enhances SASP activation, providing a mechanistic rationale for combination therapy. Based on these findings, we initiated a phase Ib/II clinical trial of mirdametinib, a MEK1/2 inhibitor, in combination with palbociclib in patients with DDLPS (NCT06843967). **Methods:** This is an ongoing phase Ib/II, single-arm, open-label, single-center study evaluating the safety, tolerability, and efficacy of mirdametinib plus palbociclib in patients with unresectable, recurrent, or metastatic DDLPS (NCT06843967). Patients may enroll at any line of therapy, including first line, consistent with contemporary palbociclib use; patients with prior CDK4/6 inhibitor exposure are eligible for the phase Ib portion. Key eligibility criteria include ECOG performance status 0–2 and RECIST v1.1–measurable disease. Phase Ib uses a Bayesian optimal interval (BOIN) design with three dose levels to determine dose-limiting toxicities, maximum tolerated dose, and recommended phase II dose (RP2D), enrolling up to 24 patients. Phase II will assess efficacy at the RP2D, with the primary endpoint of PFS at 18 weeks by RECIST v1.1 in 30 patients. Enrollment began February 19, 2025. As of January 2026, accrual is ongoing at dose level 2. Enrollment to dose level 3 is anticipated in February 2026. Clinical trial information: NCT06843967. Research Sponsor: National Cancer Institute/U.S. National Institutes of Health; 1R01CA296835–01.

SATURN-STs: Phase II study of neoadjuvant atezolizumab with doxorubicin, concurrent atezolizumab with pre-operative radiation therapy and adjuvant atezolizumab in patients with high-risk surgically resectable extremity and truncal soft tissue sarcoma.

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Background: High-risk, localized soft tissue sarcoma (STS) remains associated with high rates of distant relapse despite modern multimodality therapy. Immune checkpoint inhibition (ICI) has demonstrated activity in certain metastatic STS subtypes with signals of enhanced response when combined with doxorubicin in the advanced/metastatic setting, as well as improved disease-free survival when combined with radiotherapy (RT) in the neoadjuvant setting; however, the optimal integration of neoadjuvant chemotherapy, immunotherapy, and RT in resectable disease is unknown. This single-arm phase II trial evaluates whether neoadjuvant atezolizumab combined with doxorubicin, followed by concurrent atezolizumab with preoperative RT and adjuvant atezolizumab, can improve relapse outcomes in patients with resectable, high-risk STS of the extremity and trunk. **Methods:** SATURN-STs is an investigator-initiated phase II study enrolling 50 adults with treatment-naïve, localized, intermediate- to high-grade STS >5 cm, including undifferentiated pleomorphic sarcoma, myxofibrosarcoma, de-differentiated/pleomorphic liposarcoma, leiomyosarcoma, and unclassified sarcoma. Neoadjuvant treatment includes 4–6 cycles of doxorubicin (60–75 mg/m²) plus atezolizumab (1200 mg IV q3w), followed by atezolizumab with preoperative RT (50 Gy in 25 fractions or 42.75 Gy in 15 fractions), surgical resection, and up to 16 cycles of adjuvant atezolizumab. Radiographic imaging is performed at baseline, during neoadjuvant therapy, post-RT prior to surgery, and throughout follow-up. Longitudinal tissue is acquired for translational analyses with biopsy prior to initiation of chemoimmunotherapy and prior to RT/immunotherapy combination, followed by collection at the time of surgery. The primary endpoint is time-to-relapse (TTR), defined from time of surgical resection to the date of documented disease recurrence, compared to a historical control using a single-arm, time-to-event Bayesian monitoring approach. Secondary endpoints include objective response (RECIST 1.1), pathologic response, local recurrence-free survival, distant metastasis-free survival, progression-free survival, overall survival, and safety (CTCAE v5.0). Exploratory objectives include profiling immune microenvironment changes, genomic correlates, circulating tumor DNA, and spatial analyses. As of January 2026, 6 patients have initiated treatment at an accrual rate of 1–2 patients per month. Clinical trial registration: NCT07049848. Support: The University of Texas MD Anderson Cancer Center and Genentech Strategic Alliance Grant. Clinical trial information: NCT07049848. Research Sponsor: University of Texas MD Anderson Cancer Center and Genentech (Inc) Strategic Alliance.

Maintenance pegylated liposomal doxorubicin (PLD) versus active surveillance for advanced soft tissue sarcoma patients who had controlled disease after standard anthracycline-based treatment (MELODY).

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Background: The progression-free survival (PFS) associated with first-line chemotherapy for advanced soft tissue sarcoma (STS) remains unsatisfactory. Extending treatment with an active agent that has demonstrated clinical benefit in a patient (pt)—the maintenance therapy—may offer an opportunity to further delay disease progression. While anthracyclines are the current standard first-line treatment, their cumulative cardiotoxicity limits prolonged use. Pegylated liposomal doxorubicin (PLD) offers a more favorable cardiac safety profile, representing a viable option for extended treatment. **Methods:** MELODY is a randomized, multinational clinical trial designed to evaluate the clinical benefit of maintenance PLD in pts with advanced STS who have achieved disease control following anthracycline-based therapy. The study incorporates patient-reported outcomes (PROs) to explore the balance between extended treatment and active surveillance from the patient's perspective—providing a more holistic understanding of the value of maintenance therapy in this population. Built-in translational studies aim to identify biomarkers that better select pts most likely benefit from maintenance therapy, thereby further personalizing treatment strategies in advanced STS. Eligible criteria include advanced STS patients aged ≥ 18 who had either CR, PR, or SD after first-line anthracycline-based therapy (at least five cycles). Pts will be randomized 2:1 to the experimental arm: PLD (40 mg/m² every 28 days, up to 12 cycles) or the control arm: active surveillance. The primary endpoint is progression-free survival (PFS) post randomization. Patients in the active surveillance arm will not crossover to PLD upon progression. Secondary endpoints include QoL by EORTC C30 questionnaire, OS, 12-month PFS rate, ORR by RECIST 1.1, and time to next treatment. Left ventricular ejection fraction (LVEF) change will be an interest of safety. Exploratory objectives include efficacy endpoints (PFS, OS, 12-month PFS rate) based on circulating tumor DNA (mandatory) and FDG PET/CT SUVmax (Optional). Based on our systematic review (Lee MJ et al. *Ther Adv Med Oncol* 2025), the mPFS for the control arm is estimated to be 4 months. A clinically meaningful improvement is anticipated in the experimental arm, with a mPFS of 8 months. Assuming 80% power and an alpha level of 0.1, a total of 63 evaluable subjects are required. Accounting for an anticipated 20% drop-out rate, MELODY plans to enroll a total of 81 subjects. Clinical trial information: NCT06981637. Research Sponsor: Taiwan Oncology Cooperative Group (TCOG) of National Health Research Institute; TTY Bio-pharm Company Limited; Gene Solutions.

STARS (NCT 07265661): Surgical timing after preoperative hypofractionated radiotherapy for patients with primary localized soft tissue sarcoma of the extremity and trunk—A randomized phase 2 clinical trial.

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Background: Local management paradigm for localised soft tissue sarcoma of the extremities and trunk (ESTS) has remained relatively stable, due to the excellent outcomes associated with preoperative radiotherapy combined with limb-sparing surgery. Conventional regimens (50 Gy in 25 fractions) are effective but time-intensive and resource-demanding. Ultra-hypofractionated radiotherapy (HFRT) has emerged as a promising strategy, with comparable oncological outcomes, in preliminary retrospective analyses, prospective cohorts, and Phase II non-randomised trials. However, the optimal interval between HFRT and surgery remains undefined. **Methods:** STARS is a national, multicenter, phase II, randomized, non-inferiority trial promoted by a co-sponsorship between the Italian Sarcoma Group and the Fondazione IRCCS Istituto Nazionale dei Tumori di Milano (NCT07265661). Patients with localised, resectable ESTS scheduled for combined radiotherapy and surgery are randomized 1:1 to receive preoperative HFRT (30 Gy in 5 fractions) followed by surgery at either 1–2 weeks (Arm A) or 4–6 weeks (Arm B). Randomization is stratified by tumor size, depth, site, and comorbidities. The primary endpoint is the incidence of postoperative complications (Clavien–Dindo, any grade) within 90 days. Secondary endpoints include quality of life and patient satisfaction, oncologic outcomes (local recurrence, distant metastasis, disease-free and overall survival), pathological and radiological response, treatment-related toxicity, nutritional status, and economic impact. A concurrent observational cohort will capture outcomes of patients treated with standard approaches (surgery with/without standard radiotherapy). **Statistical Design:** A total of 142 patients (71 per arm) will be enrolled to test non-inferiority, assuming a 35% postoperative complication rate and a non-inferiority margin of 15% (one-sided $\alpha=0.05$; power 80%). Approximately 30 additional patients are expected in the observational cohort. **Significance:** STARS is the first randomized trial specifically designed to address surgical timing following HFRT in ESTS. The study is conducted within a novel co-sponsorship framework involving a national academic tertiary cancer center (Fondazione IRCCS Istituto Nazionale dei Tumori) and the leading non-profit cooperative group for rare cancers in Italy (Italian Sarcoma Group), establishing a sustainable platform for high-quality clinical research in rare diseases. By defining the safest and most effective interval between HFRT and surgery, this trial aims to optimize perioperative outcomes while enabling a shorter, patient-centered, and resource-efficient treatment pathway, informing future standards of care and guideline recommendations for localised ESTS. Clinical trial information: NCT 07265661. Research Sponsor: None.

The ATLAS study: A first-in-human phase 1/2 trial of [Ac-225]RTX-2358 in patients with relapsed or refractory soft tissue sarcoma.

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Background: Fibroblast Activation Protein (FAP) is expressed on the surface of cancer-associated fibroblasts and is involved in the formation, maintenance, and spread of tumors. Sarcoma frequently demonstrates high expression of FAP on the tumor cells themselves in contrast to other solid tumors, where it is mainly expressed on CAFs within the tumor stroma. Radioligand therapies utilizing alpha emitting isotopes such as Ac-225 have emerged as promising treatment strategies across multiple targets and indications in oncology. Ac-225 and its daughter radionuclides emit high-energy alpha particles capable of inducing double-stranded DNA breaks, leading to significant cytotoxic effects within cells. Early clinical data for other Ac-225-labeled compounds have shown promising outcomes, particularly in settings where traditional therapies have failed. [Ac-225] RTX-2358 (Ratio Therapeutics Inc, Boston, MA) is a novel FAP-targeted radioligand designed for specific high-affinity binding, resulting in prolonged tumor residence and limited normal tissue uptake. This sustained tumor retention leads to extended delivery of cytotoxic radiation to FAP-expressing tumors. A beta-emitting analog, [Lu-177]RTX-2358, has been administered to more than 25 patients under the German §13.2b compassionate use framework across multiple tumor types. Longitudinal SPECT imaging performed as late as 14 days after administration demonstrated persistent tumor retention with minimal washout. Based on time-activity curve analysis from these data, tumor biological half-time is estimated to be well in excess of 1,000 hours. Renal clearance was observed to be consistent with that reported for established lutetium-177-labeled radioligand therapies. **Methods:** This study is a seamless Phase 1 / 2 dose escalation study. The Phase 1 portion consists of a 3 x 3 dose escalation design, with patients treated in 3 planned dose escalation cohorts (7.5, 11.25 and 15 MBq) with up to 6, 8-week cycles of [Ac-225]RTX-2358. Backfill of phase 1 cohorts is permitted to facilitate selection of the recommended administered activity level for the subsequent Phase 2 expansion cohort. Dose escalation / de-escalation decisions will be made by a Safety Review Committee. Patients over 18yrs with a history of histologically confirmed relapsed or refractory soft tissue sarcoma (measurable disease per RECIST v1.1) are eligible if they have a positive [Cu-64]LNTH-1363S FAP PET, an ECOG PS 0 to 1, and adequate organ reserve and renal function. Recruitment of the first cohort was completed in December 2025. The ATLAS Study: NCT07156565 Clinical trial information: NCT07156565. Research Sponsor: None.

A phase I/II study of safety/efficacy using lurbinectedin, combined with ipilimumab, and nivolumab, for advanced soft tissue sarcomas (NCT05876715).

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Background: Soft tissue sarcoma (STS) cells exhibit heightened immunogenicity during the early stages of the disease. Therefore, immunotherapies such as ipilimumab (ipi) and nivolumab (nivo), which enhance sustained T-cell activation by suppressing regulatory T cells, are potentially more effective when administered as first-line therapy in combination with lurbinectedin—a synthetic analog of the marine alkaloid trabectedin—that not only induces apoptosis in cancer cells and exposes tumor neoantigens for immune recognition but also depletes tumor-associated macrophages, thereby restoring immune surveillance and potentially enhancing the efficacy of immunotherapy. **Methods:** This Phase I/II open-label single-site study will evaluate the safety and efficacy of lurbinectedin in combination with ipi and nivo in patients with advanced STS. Phase I patients will be previously treated, whereas phase II patients will be untreated. **Objectives:** Primary: Evaluate MTD of lurbinectedin in combination with fixed doses of ipi and nivo. Secondary: Evaluate objective response rate by RECIST v1.1 via CT/MRI/PET q 6w until end of treatment (EOT); determine progression-free survival (PFS); determine overall survival (OS). Exploratory: correlate response with amount of ctDNA via Signatera testing q 6w until EOT. **Schedule:** IV lurbinectedin q 3w (Phase I: escalating doses as per standard “cohort of three” design, 2.6 – 3.2mg/m², Phase 2: determined MTD), IV ipi 1 mg/kg q 12w, and IV nivo 3 mg/kg q 2w. Participants may continue treatment until significant disease progression or unacceptable toxicity occurs. **Key Criteria:** Inclusion: pathologic diagnosis of locally advanced unresectable or metastatic STS; measurable disease by RECIST v1.1; ECOG ≤ 1; life expectancy of ≥ 3 months; acceptable hematological status and liver/renal function. Exclusion: untreated CNS metastases; radiation therapy, targeted therapy, other antitumor treatment, or investigational drug or device study, within 2 weeks prior to study entry; chemotherapy within 21 days prior to study entry; prior exposure to anti-CTLA4 or anti-PD-1 inhibitors; pregnancy or breastfeeding; autoimmune disease, carcinomatous meningitis, systemic immunosuppression, skin rash affecting > 25% of body surface area, or inflammatory bowel disease. **Analysis:** The Intention-To-Treat population (all patients who received at least one dose of study drug) will be used for OS analysis and adverse event analysis. The Modified Intention-To-Treat population (patients who completed the first two 3-week cycles and follow-up imaging) will be used for analysis of PFS. PFS and OS will be estimated by Kaplan Meir method with two-sided 95% confidence interval. **Status:** This study has enrolled 40 patients. **Clinical trial information:** NCT05876715. **Research Sponsor:** Jazz Pharmaceuticals.